



A5327

Sofosbuvir-Containing Regimens Without Interferon For
Treatment of Acute HCV in HIV-1 Infected Individuals
(SWIFT-C)

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DA/DS ES # 11924

This file contains the current ACTG A5327 protocol, which includes the following documents, presented in reverse chronological order:

- Clarification Memorandum #1, dated 8 October 2015
- Letter of Amendment #1, dated 10 October 2016
- Clarification Memorandum #2, dated 1 November 2016
- Protocol Version 2.0, dated 2 July 2015

Clarification Memorandum #1 for:

**ACTG A5327
Sofosbuvir-Containing Regimens Without Interferon For Treatment of Acute HCV
in HIV-1 Infected Individuals (SWIFT-C)”**

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11924

Clarification Memo Date: 8 October 2015

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your IRB; however, as always, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5327 protocol if it is amended at a future date.

The following are clarifications (in bold font or strikethrough) to protocol A5327, Version 2.0, 07/02/15:

1. Section 6.3.5 is clarified as follows:

Pregnancy Test

For women with reproductive potential: a **negative urine or serum β -HCG result by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a POC/CLIA-waived test, documenting a negative result** will be required within 48 hours prior to study entry **and during study follow-up**. The test ~~should~~ **must** have a sensitivity of at least 25 mIU/mL.

~~Once a participant has enrolled with a negative documented serum pregnancy test and begins using 2 forms of contraception to prevent pregnancy, further testing per section 6.1 (during study drug dosing and in post treatment followup) can be urine testing. Urine test must have a sensitivity of at least 50 mIU/mL; if positive, must have immediate confirmation with serum β -HCG.~~

2. The first paragraph in section 10.2, Pharmacology Study Design, is clarified as follows:

Plasma and DBS will be obtained from all participants prior to initiation of SOF+RBV or LDV/SOF, at entry, weeks 1, 2, 4, 8, and 12 following SOF+RBV or LDV/SOF

initiation (weeks 8 and 12 only in those who receive 12 weeks of treatment), HCV VF **Confirmation**, and HIV-1 VF Confirmation, and premature discontinuation visits, and at weeks 2, 4, 8, and 12 post-treatment. Samples are collected prior to treatment initiation and after discontinuing treatment in the event there is a need to retrospectively evaluate the potential for ARV drug interactions or adherence, but these samples will not be analyzed a priori to limit costs.

Letter of Amendment #1 for:

ACTG A5327
Sofosbuvir-Containing Regimens Without Interferon For Treatment of Acute HCV
in HIV-1 Infected Individuals (SWIFT-C)”

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11924

Letter of Amendment Date: 10 October 2016

The following information impacts the A5327 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information also impacts the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing subjects of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

The following are changes to A5327, Version 2.0, 07/02/15 (noted in strikethrough and bold font):

The pregnancy risk summary information in the package insert for ledipasvir/sofosbuvir (Harvoni) states:

No adequate human data are available to establish whether or not HARVONI® poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of HARVONI® (ledipasvir or sofosbuvir) at exposures greater than those in humans at the recommended human dose (RHD). (Harvoni [package insert]. Foster City, CA: Gilead Sciences, Inc.; revised June 2016, section 8.1)

The prior contraception requirement of 6 months after stopping the study drugs was mainly for the participants who enrolled in Cohort 1, which was under A5327 Version 1.0, and took ribavirin (RBV) as part of their study regimen. Since the participants in Cohort 2, which is under A5327 Version 2.0, are not taking RBV the 6-month contraception requirement does not apply.

Therefore, the contraception requirement for Cohort 2 is changed to 30 days after the last dose for females and up to 90 days after the last dose for males as recommended by the manufacturer.

1. The following changes are made in Step 1 Inclusion Criteria for Cohort 2, section 4.1.13:

When participating in sexual activity that could lead to pregnancy, all participants must agree to use at least two reliable forms of **contraception** ~~contraceptive~~ simultaneously while receiving protocol-specified medications, and for **30 days** ~~6 months~~ after stopping the medications **in female participants and 90 days after stopping medications in male participants**. Such methods include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptive

2. The following changes are made in the second paragraph of the "Are there risks related to pregnancy" section of the Sample Informed Consent for Cohort 2:

Because of the potential risk involved and due to the uncertainty of risk to the fetus, you and your partner must use at least two methods of birth control that you discuss with the study staff. You must continue to use both methods ~~until~~ **for 30 days** ~~6 months~~ after stopping study drugs **for women and 90 days after stopping study drugs for men**. You must choose two or more of the birth control methods listed below:

- A condom (male or female) with or without a spermicide
- Diaphragm or cervical cap with spermicide
- An intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptives

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

Clarification Memorandum #2 for:

**ACTG A5327
Sofosbuvir-Containing Regimens Without Interferon For Treatment of Acute HCV
in HIV-1 Infected Individuals (SWIFT-C)”**

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11924

Clarification Memo Date: 1 November 2016

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your IRB; however, as always, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5327 protocol if it is amended at a future date.

The following are clarifications (in bold font or strikethrough) to protocol A5327, Version 2.0, 07/02/15:

1. Section 6.3.5 is clarified as follows:

Pregnancy Test

For women with reproductive potential: a **negative urine or serum β -HCG result by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a POC/CLIA-waived test, documenting a negative result** will be required within 48 hours prior to study entry **and during study follow-up**. The test ~~should~~ **must** have a sensitivity of at least 25 mIU/mL.

~~Once a participant has enrolled with a negative documented serum pregnancy test and begins using 2 forms of contraception to prevent pregnancy, further testing per section 6.1 (during study drug dosing and in post treatment followup) can be urine testing. Urine test must have a sensitivity of at least 50 mIU/mL; if positive, must have immediate confirmation with serum β -HCG.~~

2. The first paragraph in section 10.2, Pharmacology Study Design, is clarified as follows:

Plasma and DBS will be obtained from all participants prior to initiation of SOF+RBV or LDV/SOF, at entry, weeks 1, 2, 4, 8, and 12 following SOF+RBV or LDV/SOF initiation (weeks 8 and 12 only in those who receive 12 weeks of treatment), HCV VF **Confirmation**, and HIV-1 VF Confirmation, and premature discontinuation visits, and at weeks 2, 4, 8, and 12 post-treatment. Samples are collected prior to treatment initiation and after discontinuing treatment in the event there is a need to retrospectively evaluate the potential for ARV drug interactions or adherence, but these samples will not be analyzed a priori to limit costs.

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CONTENTS

	Page
SITES PARTICIPATING IN THE STUDY	4
PROTOCOL TEAM ROSTER	5
STUDY MANAGEMENT	8
GLOSSARY OF PROTOCOL-SPECIFIC TERMS	10
SCHEMA	12
 1.0 HYPOTHESIS AND STUDY OBJECTIVES	 14
1.1 Hypothesis	14
1.2 Primary Objectives	14
1.3 Secondary Objectives	14
 2.0 INTRODUCTION	 15
2.1 Background	15
2.2 Rationale	17
2.3 Rationale for Inclusion of Concomitant ARV Regimens	47
2.4 Spontaneous Clearance of HCV	48
2.5 Overall Risk/Benefit Assessment	49
2.6 Adherence Measures	49
 3.0 STUDY DESIGN	 49
 4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS	 50
4.1 Step 1 Inclusion Criteria for Cohort 2	50
4.2 Step 1 Exclusion Criteria for Cohort 2	54
4.3 Step 2 Inclusion Criteria for Cohort 2	55
4.4 Step 2 Exclusion Criteria for Cohort 2	55
4.5 Study Enrollment Procedures	56
4.6 Coenrollment Guidelines	56
 5.0 STUDY TREATMENT	 57
5.1 Regimens, Administration, and Duration	57
5.2 Study Product Formulation	58
5.3 Pharmacy: Product Supply, Distribution, and Accountability	59
5.4 Concomitant Medications	59
 6.0 CLINICAL AND LABORATORY EVALUATIONS	 61
6.1 Schedule of Events	61
6.2 Timing of Evaluations	68
6.3 Instructions for Evaluations	70
 7.0 CLINICAL MANAGEMENT ISSUES	 77
7.1 Toxicity	77
7.2 Pregnancy	80
7.3 HCV Virologic Response-Based Stopping Criteria	81
7.4 HIV-1 Treatment Failure	81

CONTENTS (Cont'd)

8.0	CRITERIA FOR DISCONTINUATION	82
8.1	Permanent Treatment Discontinuation	82
8.2	Premature Study Discontinuation	82
9.0	STATISTICAL CONSIDERATIONS	83
9.1	General Design Issues	83
9.2	Outcome Measures	84
9.3	Randomization and Stratification	85
9.4	Sample Size and Accrual	85
9.5	Monitoring	88
9.6	Analyses	88
10.0	PHARMACOLOGY PLAN	89
10.1	Pharmacology Objectives	90
10.2	Pharmacology Study Design	91
10.3	Primary and Secondary Data, Modeling, and Data Analysis	91
10.4	Anticipated Outcomes	91
11.0	DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING	92
11.1	Records to Be Kept	92
11.2	Role of Data Management	92
11.3	Clinical Site Monitoring and Record Availability	92
11.4	Expedited Adverse Event Reporting to DAIDS	93
12.0	PARTICIPANTS	94
12.1	Institutional Review Board (IRB) Review and Informed Consent	94
12.2	Participant Confidentiality	94
12.3	Study Discontinuation	94
13.0	PUBLICATION OF RESEARCH FINDINGS	94
14.0	BIOHAZARD CONTAINMENT	94
15.0	REFERENCES	96

APPENDIX I: SCREENING FLOW CHART FOR ACUTE HCV INFECTION

APPENDIX II: SAMPLE INFORMED CONSENT **FOR COHORT 1**

APPENDIX III: SAMPLE INFORMED CONSENT FOR COHORT 2

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A5327/SWIFT-C is a multicenter study open only to US ACTG clinical research sites (CRSs).

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.coreA5327@fstfr.org via e-mail. The appropriate team member will respond with a "cc" to actg.coreA5327@fstfr.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group

Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the [actg.protA5327](mailto:actg.protA5327@fstfr.org) e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstfr.org

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol core team. Send an e-mail message to actg.coreA5327@fstfr.org (ATTN: Susanna Naggie and Raymond Chung). Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory

For questions specifically related to virologic and pharmacologic laboratory tests, contact Victoria Johnson (virologist) and Jennifer Kiser (pharmacologist), respectively. Send an e-mail message to actg.coreA5327@fstfr.org.

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.fstfr.org.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Laura Weichmann directly.
- For other questions, send an e-mail message to actg.coreA5327@fstfr.org (ATTN: Laura Weichmann).
- Include the protocol number, PID, and a detailed question.

Participant Registration

For **participant** registration questions or problems and study identification number SID lists.

- Send an e-mail message to rando.support@fstfr.org. Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at **716-834-0900 x7301**.

Computer and Screen Problems

Contact the SDAC/DMC programmers.

- Send an e-mail message to actg.support@fstfr.org or call 716-834-0900 x7302.

Protocol Document Questions

For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.coreA5327@fstfr.org (ATTN: **Jhoanna Roa**).

STUDY MANAGEMENT (Cont'd)

Copies of the Protocol

To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (<https://www.actgnetwork.org>).

Product Package Inserts and/or Investigator Brochures

To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration

For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Study Product

For questions or problems regarding study product, dose, supplies, records, and returns, call Thucuma Sise, protocol pharmacist, at 301-496-8213.

Study Drug Orders

Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

Expedited Adverse Event (EAE) Reporting/Questions

Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls

Sites are responsible for documenting any phone calls made to A5327 team members. Send an e-mail to actg.coreA5327@fstf.org.

Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

3TC	lamivudine
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
AST	aspartate aminotransferase (also SGOT)
ATV	atazanavir
AUC	area under the curve
AUC _{tau}	area under the plasma concentration versus time curve over the dosing interval
BMI	body mass index
BOC	boceprevir
CAP	College of American Pathologists
CHC	chronic hepatitis C
CKD	chronic kidney disease
C _{max}	maximum observed concentration of drug
CLIA	Clinical Laboratory Improvement Amendments
COBI	cobicistat
CrCl	creatinine clearance
CSA	colony stimulating agents
C _{tau}	observed drug concentration at the end of the dosing interval (tau)
d4T	stavudine
DAA	direct acting antiviral
DBS	dried blood spots
ddl	didanosine
DRV	darunavir
DTG	dolutegravir
ECG	electrocardiogram
EFV	efavirenz
E _{max}	maximal effect
EVG	elvitegravir
FDC	fixed dose combination
FTC	emtricitabine
GT	genotype (viral)
HBV	hepatitis B virus
HCV	hepatitis C virus
ICH	International Conference on Harmonisation
IFN	interferon
IL28B	IL28B gene
ISGs	IFN stimulated genes
ITT	intention-to-treat
LLOQ	lower limit of quantification

GLOSSARY OF PROTOCOL-SPECIFIC TERMS (Cont'd)

LDV	ledipasvir
LDV/SOF	ledipasvir/sofosbuvir
Hg	mercury
PBMC	peripheral blood mononuclear cell(s)
PEG-INF	pegylated interferon
P-gp	P-glycoprotein
PI	protease inhibitor
POC	point-of-care
r	low dose ritonavir (booster)
RBV	ribavirin
RPV	rilpivirine
RTV	ritonavir
RVR	rapid virologic response
SOF	Sofosbuvir, GS-7977
SVR	sustained virologic response
TAF	tenofovir alafenamide
TFV	tenofovir
TDF	tenofovir disoproxil fumarate
TND	target not detected
TPV	tipranavir
TVR	telaprevir
t _{1/2}	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of the normal range
ZDV	zidovudine

SCHEMA

A5327

Sofosbuvir-Containing Regimens without Interferon for Treatment of Acute HCV in HIV-1 Infected Individuals (SWIFT-C)**DESIGN**

SWIFT-C is a Phase I, open-label, two-cohort clinical trial, in which between 44 and 50 acutely HCV-infected HIV-1 positive **participants** will be enrolled and administered oral sofosbuvir (SOF) in combination with weight-based ribavirin (RBV, **cohort 1**) or **ledipasvir (LDV, cohort 2)**.

The study will investigate the safety and efficacy of two SOF-containing regimens and will assess if the addition of a second DAA allows for a shortened course of therapy. The study will open the first cohort **with sofosbuvir plus ribavirin (SOF+RBV)** for 12 weeks and with a planned accrual of at least 17 **participants**. The second cohort will open **with ledipasvir/sofosbuvir (LDV/SOF) for an 8-week treatment**. The second cohort will include at least 27 **participants**. Each cohort will occur in two steps: on treatment (Step 1) and followup (Step 2). See Figure 1. The cohorts will enroll sequentially.

DURATION

32-36 weeks (8-12 weeks on-treatment followed by 24 weeks of follow-up)

SAMPLE SIZE

A minimum of 44 **participants** will be enrolled in **Cohort 1 and Cohort 2**.

Cohort 1: Minimum of 17 participants will be enrolled.

Cohort 2: Minimum of 27 participants will be enrolled.

If a **participant** is discontinued from study treatment for non-virologic reasons or is not evaluable for SVR12 while enrollment is ongoing to the same cohort, then an additional **participant** may be enrolled to that cohort to help ensure that an adequate number complete study treatment and are evaluable for SVR12, up to a maximum enrollment of 50 **participants**.

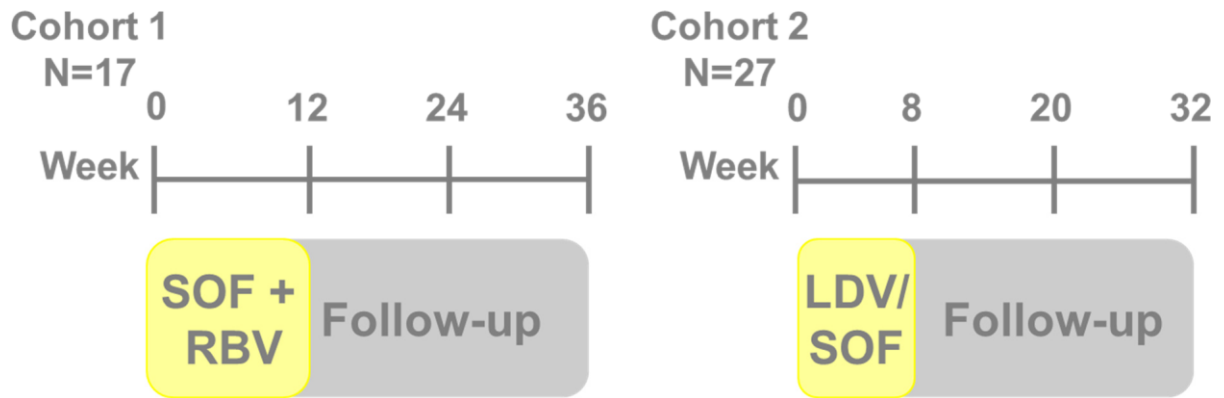
POPULATION

HIV-1 coinfecting individuals who have acute HCV infection or reinfection **and have any genotype (Cohort 1) and genotype 1 or 4 (Cohort 2)**.

REGIMEN

Cohort 1: SOF 400mg once daily and weight-based RBV (1000 or 1200 mg daily in two divided doses)

Cohort 2: Daily fixed dose combination pill of LDV/SOF (90mg/400mg)



1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

An interferon-sparing regimen of sofosbuvir (SOF) and ribavirin (RBV) **and/or ledipasvir/sofosbuvir (LDV/SOF)** can achieve sustained virologic response (SVR)12 rates that are noninferior to the current standard of care assessed by historical control for the treatment of acute HCV in HIV-1/HCV co-infected individuals with an improved safety profile and a shorter length of treatment.

1.2 Primary Objectives

- 1.2.1 To evaluate HCV treatment response to SOF and weight-based RBV (1000 or 1200 mg daily in two divided doses) taken for 12 **weeks and daily LDV/SOF taken for 8 weeks** as assessed by SVR12, defined as HCV RNA undetectable [$<$ lower of limit of quantification (LLOQ) target not detected (TND)] 12 weeks post-treatment in persons with existing HIV-1 infection who are acutely infected with any HCV genotype (**Cohort 1**) or **Genotype 1 or 4 (Cohort 2)**.
- 1.2.2 To evaluate the safety and tolerability of combination oral antiviral therapy with SOF and weight-based RBV taken for 12 **weeks and daily LDV/SOF taken for 8 weeks** in persons with existing HIV-1 infection who are acutely infected with any HCV genotype (**Cohort 1**) or **Genotype 1 or 4 (Cohort 2)**.

1.3 Secondary Objectives

- 1.3.1 To evaluate the antiviral efficacy of SOF and weight-based RBV **and LDV/SOF** as measured by the proportion of **participants** with HCV RNA undetectable ($<$ LLOQ TND) at weeks 1, 2, 4, 8, 12, and at 2 (SVR2), 4 (SVR4), 8 (SVR8), 12 (SVR12), and 24 (SVR24) weeks post-treatment.
- 1.3.2 To evaluate evidence of relapse, defined as HCV RNA undetectable ($<$ LLOQ TND) at end-of-treatment but HCV RNA quantifiable (\geq LLOQ) during followup.
- 1.3.3 To assess the emergence of viral resistance to SOF **and LDV** when administered for acute HCV infection.
- 1.3.4 To estimate RBV pharmacokinetics (PK) and evaluate covariates (including concomitant antiretroviral drugs) which may affect RBV PK. (**Cohort 1 only**)
- 1.3.5 To assess the relationship of viral clearance and RBV PK (**Cohort 1**) with baseline predictors including genetic polymorphisms (eg, IL28B and ITPA), expression of key host immune response genes and proteins.
- 1.3.6 **To assess the effects of LDV on the PK of tenofovir (TFV) in persons on tenofovir disoproxil fumarate (TDF)-containing regimens. (Cohort 2 only)**

- 1.3.7 To evaluate **participants'** adherence by using several tools, including self-report, pill count, and **drug** concentrations.
- 1.3.8 To evaluate the hypothesis that successful direct-acting antiviral (DAA)-based therapy alleviates type I interferon (IFN)-induced immune dysfunction during acute HCV infection.

2.0 INTRODUCTION

2.1 Background

Hepatitis C virus (HCV) infection affects more than 4 million persons and causes an estimated 12,000 deaths annually in the United States [Armstrong, 2006]. The projected burden to our society from chronic HCV infection from 2010 to 2019 has been estimated to exceed \$10.7 billion in direct medical costs, \$54.2 billion in premature mortality costs, and \$21.3 billion in costs from morbidity due to disability [Wong, 2000]. The Centers for Disease Control and Prevention (CDC) estimate that there are close to **17,000** new cases of acute HCV per year, although only 700-800 are reported (www.cdc.gov/hepatitis/Statistics/index.htm), last accessed June 12, 2013]. Early identification of acute HCV infection is essential to prevent chronic infections and the long-term liver disease complications that may occur. Early identification and treatment of HCV during the acute phase can result in significantly higher response rates with shorter durations of therapy. This is true in HCV monoinfected and HIV/HCV coinfecting individuals [Jaeckel, 2001; Corey, 2010; Matthews, 2009; Boesecke, 2011].

There is currently no accepted standard regimen for the management of acute HCV. Studies have included standard IFN monotherapy, pegylated interferon (PEG-IFN) monotherapy, and PEG-IFN in combination with RBV (both standard and weight-based dosing) [Jaeckel, 2001; Corey, 2010; Matthews, 2009; Boesecke, 2011]. A meta-analysis of HCV monoinfected **participants** with acute HCV infection (N=602) reported an overall SVR of 78%, which was significantly higher than those **participants** not receiving any therapy (55%, OR=3.08; 95% CI 1.8-4.8) [Corey, 2010]. A majority of **participants** were treated with PEG monotherapy with an average duration of therapy of 19.7 weeks. This analysis also reported that those **participants** who initiated treatment within the first 12 weeks of diagnosis had the highest SVR rates. Across all studies included in the analysis, 44% of **participants** diagnosed with acute HCV (N=473) did not receive any therapy primarily due to participant deferment of therapy, contraindications to therapy, or spontaneous viral clearance prior to treatment initiation. In this meta-analysis, spontaneous clearance rates were higher than has been historically described and is likely because a majority of these **participants** were symptomatic and thus more likely to spontaneously clear. Jaundice on presentation has been previously associated with spontaneous clearance, a presentation more commonly seen in **participants** with the favorable IL28B CC genotype, a single nucleotide polymorphism associated with spontaneous clearance [Gerlach, 2003; Tillman, 2010]. Yet, approximately 50% of the **participants** did not resolve the infection and did not receive therapy. Furthermore, treatment responses in HIV-1/HCV coinfecting **participants** have been lower than those reported in acute HCV monoinfection. The largest prospective study of acute HCV

treatment in HIV-infected individuals to date is from the European AIDS Treatment Network (NEAT), which included 36 **participants** and reported an SVR of 61% [Vogel, 2006]. This study suggests that there is a need for improved regimens that will be more acceptable to **participants** and better tolerated than IFN.

In the past **two years**, curative IFN-sparing regimens have been realized for both HCV genotype 1 and genotype 2/3 chronic infections and in both treatment-naïve and treatment-experienced **participants**. **SOF, a nucleotide analogue of the HCV polymerase, was approved by the United States Food and Drug Administration (US FDA) in December 2013.** The Phase 3 FISSON, FUSION, POSITRON, and VALENCE studies investigated SOF in treatment-naïve and -experienced **participants** with chronic HCV genotype 2/3 infection [Jacobson, 2013; Lawitz, 2013; Zeuzem, 2013]. In treatment-naïve and IFN-unable genotype 2 and 3 **participants** who received 12 weeks of treatment, SVR12 rates were 93-97% and 56-61%, respectively. In treatment-experienced **participants** who received 12 and 16 weeks of therapy, SVR12 rates were 86% and 94% in genotype 2 **participants** and 30% and 62% in genotype 3 **participants**, respectively. In treatment-naïve and -experienced **participants** who received 24 weeks of treatment, SVR12 was 85%. The PHOTON-1 **and 2 Phase 3 studies investigated** SOF with RBV for 12 weeks in genotype 2 treatment-naïve **HIV-1 co-infected participants and for 24 weeks in treatment-naïve genotype 3 and treatment-experienced genotype 2 or 3 HIV-1 coinfecting participants. The studies also evaluated 24 weeks of SOF+RBV in genotype 1 treatment-naïve HIV-1 coinfecting participants. A pooled analysis of the SVR12 results was** recently presented at American Association for the Study of Liver **Diseases Meeting in Boston, MA.** SVR12 was achieved by **81%, 89%, and 91%** of genotype 1, 2, and 3 **treatment-naïve participants**, respectively [Rockstroh, 2014]. The ELECTRON study investigated the feasibility of using an IFN-free approach to the treatment of chronic genotype 1, 2, and 3 infection in **HIV negative participants** [Gane, 2013]. The combination of SOF with RBV for 12 weeks resulted in 84% SVR12 in treatment-naïve genotype 1 **participants**. The SPARE trial investigated the combination of SOF with RBV for 24 weeks in treatment-naïve genotype 1 **participants** who had more difficult-to-treat baseline characteristics than in many registration trials, including 72-92% African-American race and up to 28% cirrhosis [Osinusi, 2013]. The largest trial of this IFN-free combination regimen reported SVR24 of 68% in this very difficult-to-treat patient population.

The IFN and RBV-free fixed dose combination of LDV (an NS5A inhibitor) and SOF was approved for the treatment of chronic genotype 1 HCV infection in October 2014 [Harvoni PI, 2015]. The Phase 3 ION studies (ION-1, 2, 3, 4) investigated the safety and efficacy of LDV/SOF in participants chronically infected with genotype 1 and included treatment-naïve (ION-1 and ION-3) and -experienced (ION-2)/participants with cirrhosis (ION-1 and ION-2)/and participants with HIV co-infection (ION-4) [Harvoni PI, 2015; Naggie, CROI 2015 abstract LB152]. Overall SVR12 rates were high (>93%) across the Phase 3 program. Specifically, the ION-3 study investigated 8 or 12 weeks of LDV/SOF in treatment-naïve participants. The 8-week arm was non-inferior compared to the 12-week arm, although there were more relapses (5% vs. 1%, respectively). A subgroup analysis suggested that among participants with a baseline HCV RNA <6 million IU/mL, the SVR12 was

97% in the 8-week arm and 96% in the 12-week arm, suggesting specific patient populations may be able to achieve high SVR12 with just 8 weeks of LDV/SOF.

To date over **5,000 HCV-infected participants** have been dosed with SOF either in combination with PEG/RBV, RBV or alone as monotherapy and to date, no on-treatment viral breakthrough has occurred in any **participant**. However, approximately 230 **participants** have experienced relapse after cessation of SOF-containing regimens [Gane, 2013; Jacobson, 2013; Lawitz, 2013]. Population sequencing identified only one **participant** (genotype (GT) 2b who had received SOF monotherapy) with the S282T mutation and this did confer decreased susceptibility to SOF. Deep sequencing did not identify this mutation in any other **participant** [Gane, 2013; Jacobson, 2013; Lawitz, 2013]. **Similarly, of over 1600 participants treated with LDV/SOF in the Phase 3 program, no participant developed the S282T mutation.** These results confirm that SOF has an exceptionally high barrier to resistance. Thus, **SOF-containing regimens appear** to be ideal for the treatment of acute HCV infection. Its broad efficacy across HCV genotypes, once daily dosing regimen, and minimal side effects profile could significantly increase uptake for treatment of acute HCV infection and provide similar, if not improved, efficacy over the current standard of care. **The addition of LDV does increase the risk of developing resistance mutations at time of virologic failure. Of the over 1600 participants treated in the Phase 3 program, 1.8% had detected resistant variants in the NS5A region at the time of failure. Thus, with SOF as a backbone in this combination regimen, the risk of virologic failure is extremely low as is the risk of resistant variants [Harvoni PI, 2015].**

The original study design of A5327 involved a 2-cohort clinical trial that planned to enroll participants sequentially using the same regimen of SOF+RBV with the potential to shorten the therapy from 12 to 8 weeks if a predetermined interim analysis found that SVR4 rates for the 12-week arm achieved non-inferiority as compared to a historic control. Due to the small sample size of cohort 1, the lower end of the non-inferiority margin would allow for only 3 virologic failures. Cohort 1, which investigated SOF+RBV for 12 weeks, has reported 7 viral failures to date, all due to relapse after end of treatment. Although the prior study design would have continued to enroll participants on SOF+RBV for 12 weeks to improve the power to achieve non-inferiority, it was felt by the protocol team that this would have resulted in potentially unacceptable SVR rates and that significant advancements in HCV therapeutics since the initial design of the trial required implementation of more contemporary and effective therapies. Specifically, the availability of oral, DAA combination therapies would provide the possibility of higher efficacy and the same excellent safety. Thus, a protocol amendment was pursued to change the regimen for cohort 2 from SOF+RBV to LDV/SOF. Because of existing data demonstrating that 8 weeks of LDV/SOF is safe and effective in select chronically HCV infected participants, this was felt to be the ideal length of treatment for acute infection.

2.2 Rationale

HIV infection treatment has improved with the widespread availability of antiretrovirals (ARVs) and the appearance of numerous drugs in the market over the past 15 years.

Currently, several ritonavir (RTV) (r)-boosted PIs in combination with other ARVs are recommended as options for first-line ARV therapy, and several are approved for and commonly used in treatment-experienced **patients**. While extremely effective for treatment of HIV, r-boosted PIs are substrates for and potent inhibitors of cytochrome P450 3A4 (CYP 3A4) enzymes; as a result, drug-drug interactions with these agents are frequent. Numerous PK studies and case reports provide evidence that r-boosted PIs are associated with a number of clinically relevant drug interactions as a result of PK changes related to either the PI or the concomitant medications. Other first-line ARV therapies include non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase inhibitors in combination with nucleoside or nucleotide reverse transcriptase inhibitors (NRTI). These non-nucleoside inhibitors, in particular efavirenz (EFV), are substrates and inducers of CYP-450 2B6 and 3A4. [Panel on ARV Guidelines for Adults and Adolescents 2012; Asboe, 2012]

Thus far, HCV PIs are substrates and inhibitors of CYP3A4, and therefore have significant drug interactions with the ARV therapies [Seden, 2010]. Drug interactions with both TVR and BOC and ritonavir (RTV) boosted PIs, have been reported and in some cases have been contraindicated for combined use [Van Heeswijk, 2011; Hulskotte, 2012; Sulkowski, 2013d; Sulkowski, 2013e]. Drug interaction studies have also been reported between both drugs with EFV whereby exposures of both TVR and BOC are reduced [Van Heeswijk, 2011; Hulskotte, 2012; de Kanter, 2012; Sulkowski, 2013d; Sulkowski, 2013e]. Thus, there is a tremendous need for direct-acting antivirals (DAAs) with reduced potential for drug interactions with ARV.

SOF exhibits several attractive characteristics for combining with ARVs. SOF itself is a prodrug, requiring intracellular phosphorylation to a uridine triphosphate to exert antiviral effects. Multiple studies suggest a lack of involvement of SOF and its metabolites with the metabolic enzymes involved in xenobiotic transformation, and hence, demonstrate that metabolically based drug interactions with SOF are unlikely. In vitro assays indicate that SOF is a substrate but not an inhibitor of **the** drug transporters, P-gp and BCRP, and is not a substrate of OATP. SOF concentrations may be increased by drugs that inhibit these transporters (eg, cyclosporine), but **concentrations of** the primary circulating metabolite in plasma, GS-331007, are unaffected. **Similarly, LDV is not an inhibitor or inducer of major drug metabolizing enzyme systems, and is unlikely to be a perpetrator of cytochrome P450 enzyme (CYP) or UGT1A1-mediated drug-drug interactions. LDV may be affected by transporter-related drug-drug interactions. LDV is a substrate for intestinal efflux transporters and is an inhibitor of the intestinal efflux transporters BCRP and Pgp. LDV is not a substrate for hepatic uptake transporters (OCT1, OATP1B1, and OATP1B3). LDV is an inhibitor of the hepatic transporters OATP1B1 and OATP1B3. In general, LDV has a low potential for drug interactions.**

HCV infection has been associated with early induction of a type I IFN program, which in turn results in successful spontaneous clearance by virtue of induction of an endogenous antiviral program, but with early chronicity appears to exert counterproductive effects that include T cell dysfunction/hypofunction/exhaustion. Exciting data **support** that abrogation of the type I program can restore dysfunctional

immunity and revert IFN stimulated genes (ISGs) to baseline in chronic infection (Wilson 2013; Teijaro 2013). With IFN-sparing regimens, the study team can now evaluate this hypothesis in early, acute infection and compare **participants** who successfully clear infection from those who do not. The study team will compare ISGs using customized Nanostring arrays from PBMCs prior to and at the end of treatment and followup and correlate with corresponding HCV specific functional assays (CD4 proliferative and CD8 CTL assays) between sustained responders (expected to be about 85% of the group) and nonresponders/relapsers (expected to be about 15% of the group). The study team will also correlate with circulating IP-10, a type I IFN stimulated cytokine. To enhance the numbers of nonresponders and progressors to chronicity, the study team will also evaluate a unique cohort of 20 acutely HCV-infected **participants** with preexisting HIV infection whose serial PBMCs were collected as part of an ongoing MGH HCV immunology longitudinal repository and who progressed to chronic infection. Thus, the study team has the unique and ideal ability to assess whether early immune dysfunction can be abrogated with successful DAA therapy. The study team will also be able to analyze the ISG induction patterns at baseline prior to therapy as a function of IL28B genotype, since we hypothesize that a more elevated ISG induction pattern may be associated with less favorable IL28B genotype. These findings will have strong implications for recommendations for early treatment of acutely infected patients, since immune preservation may be reliant on it.

SOF in combination with RBV has been shown to be safe and effective in patients with genotype 1-4 infections and the limited drug interaction profile and extremely limited risk of NS5B resistance makes this an ideal regimen for the treatment of acute hepatitis C in HIV/HCV co-infected persons. However, the recent approval of DAA combinations that are IFN- and RBV-free are also of great interest. The addition of other DAA into combination regimens may slightly increase the risk of drug interactions and resistance, but the exceptional safety and efficacy profiles makes these regimens preferred to a 12-week regimen of SOF+RBV. Moreover, data for some DAA combinations in chronic HCV support truncation of therapy in persons with favorable characteristics, including absence of cirrhosis and lower viral loads. Coupled with historic experience that shorter regimens of antiviral therapy can produce high rates of response in acute infection, there is strong rationale to investigate shorter courses of these DAA-based regimens in patients with acute HCV infection.

2.2.1 Use of Sofosbuvir

The efficacy of SOF was evaluated in seven Phase 3 trials in a total of 1724 HCV mono-infected participants with genotypes 1 to 6 chronic hepatitis C (CHC) and 497 HIV/HCV co-infected participants with genotypes 1 to 4. Six of the trials investigated SOF in combination with RBV and included HCV mono-infected participants with genotype 2 or 3 infection and HIV/HCV co-infected participants with genotype 1 to 4 infection. Participants in these trials had compensated liver disease including cirrhosis. SOF was administered at a dose of 400 mg once daily and the RBV dose was weight-based 1000-1200 mg daily administered in two divided doses.

2.2.1.1 Clinical Efficacy in Participants with Genotype 1 HCV infection and HIV Co-infection

SOF was studied in an open-label clinical trial in North America and Puerto Rico evaluating the safety and efficacy of 12 or 24 weeks of treatment with SOF+RBV in participants with genotype 1, 2, or 3 CHC coinfecting with HIV-1. Genotype 2 and 3 participants were either HCV treatment-naïve or treatment-experienced, whereas genotype 1 participants were all treatment-naïve. Participants received 400 mg SOF and weight-based RBV (1000 mg for participants weighing <75 kg or 1200 mg for participants weighing ≥75kg) daily for 12 or 24 weeks based on genotype and prior treatment history. Participants were either not on antiretroviral (ARV) therapy with a CD4+ cell count >500 cells/mm³ or had virologically suppressed HIV-1 on ARV therapy with a CD4+ cell count >200 cells/mm³. Table 2-1 presents the available efficacy data 12 weeks post treatment for 210 of the 223 enrolled participants [Sulkowski, 2014].

Table 2-1: Response Rate in PHOTON-1

	HCV Genotype 1 Treatment-Naïve	HCV Genotype 2/3 Treatment-Naïve	HCV Genotype 2/3 Treatment- Experienced
	SOF+RBV 24W N=114	SOF+RBV 12W N=68	SOF+RBV 24W N=28
Overall SVR	76% (87/114)	75% (51/68)	93% (26/28)
On treatment failure	1% (1/114)	1% (1/68)	0/28
Relapse	22% (25/113)	18% (12/67)	7% (2/28)
Other	1% (1/114)	6% (4/68)	0/28

The SVR rate was 82% (74/90) in participants with genotype 1a infection and 54% (13/24) in participants with genotype 1b infection. SVR rates in participants with HCV genotype 1 infection were 80% (24/30) in participants with baseline IL28B C/C allele and 75% (62/83) in participants with baseline IL28B non-C/C alleles [Sulkowski, 2014].

In the 223 enrolled participants, the CD4+ cell percentage did not change during treatment. Median CD4+ cell count decreases of 85 cells/mm³ and 84 cells/mm³ were observed at the end of treatment with SOF+RBV for 12 or 24 weeks, respectively. HIV-1 rebound during SOF+RBV treatment occurred in 2 participants (0.9%) on ARV therapy.

2.2.1.2 Clinical Efficacy in HCV Mono-infection

In the SOF Phase 3 clinical program, the SOF+RBV treatment regimen for 12 or 16 weeks was evaluated in **participants** with genotype 2 or 3 HCV infection and the SOF+PEG+RBV treatment regimen for 12 weeks was evaluated in **participants** with genotype 1, 4, 5, or 6 HCV infection. Across all relevant HCV genotypes and multiple patient populations, SOF, in combination with RBV with or without PEG demonstrated similar or superior efficacy to currently available treatment.

All Phase 3 studies in **participants** with genotype 2 or 3 HCV infection demonstrated efficacy, achieving their primary endpoints in each study. Study P7977-1231 met its primary efficacy endpoint of noninferiority of treatment with SOF+RBV for 12 weeks compared with the current standard-of-care, PEG+RBV for 24 weeks (approximately 67% of **participants** achieving a SVR12 for both treatments). Study GS-US-334-0107 met its primary efficacy endpoint of superiority of treatment with SOF+RBV for 12 weeks compared with placebo (77.8% of **participants** achieved SVR12 in the SOF+RBV group versus 0% in the placebo group [$p<0.001$]). Study GS-US-334-0108 met its primary efficacy endpoint of superiority of treatment with SOF+RBV for both 12 and 16 weeks compared with an historic control SVR12 rate of 25% (50.0% and 72.6% of **participants** achieved SVR12 in the SOF+RBV 12 and 16 Week groups, respectively [$p<0.001$ for both groups]). As has been described previously for IFN-based treatment, response rates were higher in **participants** with genotype 2 HCV infection compared with **participants** with genotype 3 HCV infection.

Study GS-US-334-0110 met its primary efficacy endpoint for superiority of SOF+PEG+RBV treatment for 12 weeks (90.2% of **participants** achieving a SVR12) compared with a predefined historic control SVR rate (60%; $p<0.001$).

In a pooled analysis of 991 participants who received SOF in four Phase 3 trials (NEUTRINO, FISSION, POSITRON, and FUSION), 226 participants qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA >1000 IU/mL. Post-baseline NS5B sequences were available for 225 of the 226 participants, with deep sequencing data (assay cutoff of 1%) from 221 of these participants. The SOF-associated resistance substitution S282T was not detected in any of these participants by deep sequencing or population sequencing. However, an S282T substitution was detected in one genotype 2b participant who relapsed at Week 4 post-treatment after 12 weeks of SOF monotherapy in the Phase 2 trial P7977-0523 [ELECTRON]. The isolate from this participant displayed a mean 13.5-fold reduced susceptibility to SOF. For this participant, the S282T substitution was no longer detectable at Week 12 post-treatment

by next generation sequencing with an assay cut off of 1%. No other NS5B substitutions were identified to be associated with resistance to SOF by deep sequencing and phenotypic analyses [Sovaldi PI, 2015].

2.2.1.3 Clinical Safety

The primary safety data for this clinical safety section are derived from the 4 pivotal Phase 3 studies P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-344-0108 (FUSION), and GS-US-334-0110 (NEUTRINO), with supporting safety data from Phase 2 studies as appropriate.

2.2.1.3.1 Adverse Events

Adverse events (AEs) comprised any events with onset dates on or after the date of the first dose of any study drug up to 30 days after the last dose of any study drug.

2.2.1.3.2 Overall Summary of Adverse Events

Table **2-2** provides an overall summary of AEs reported in the 4 pivotal Phase 3 studies. The placebo group had the lowest proportion of AEs (77.5%) and the PEG+RBV group had the highest proportion of AEs (95.9%) compared with the SOF+RBV groups (approximately 88%). Similarly, the placebo group had the lowest (1.4%) and the PEG+RBV group had the highest (18.5%) proportion of Grade 3 or 4 AEs compared with the SOF+RBV groups (4.1-7.2%). This trend was also observed for Grade 2 and higher AEs. The PEG+RBV group had the highest proportion of **participants** who had an AE that led to permanent discontinuation from any study drugs (11.9%) compared with all other groups. One death (cocaine and heroin overdose on Day 1 in the SOF+RBV 12 Week group) was reported.

Table 2-2: Overall Summary of Adverse Events in the Pivotal Phase 3 Studies
(Safety Analysis Set)

	GS-US-334-0107 (POSITRON)	P7977-1231 (FISSION) GS-US-334-0107 (POSITRON) GS-US-334-0108 (FUSION)	GS-US-334-0108 (FUSION)	P7977-1231 (FISSION)	GS-US-334-0110 (NEUTRINO)
	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any:					
AE	55 (77.5%)	496 (87.6%)	86 (87.8%)	233 (95.9%)	310 (94.8%)
Grade 3 or 4 AE	1 (1.4%)	41 (7.2%)	4 (4.1%)	45 (18.5%)	48 (14.7%)
Grade 2 and Higher AE	21 (29.6%)	238 (42.0%)	41 (41.8%)	167 (68.7%)	194 (59.3%)
Treatment-Related AE	40 (56.3%)	408 (72.1%)	75 (76.5%)	228 (93.8%)	304 (93.0%)
Grade 3 or 4 Treatment-Related AE	0	15 (2.7%)	2 (2.0%)	39 (16.0%)	42 (12.8%)
Grade 2 and Higher Treatment-Related AE	12 (16.9%)	161 (28.4%)	22 (22.4%)	149 (61.3%)	175 (53.5%)
Any SAE	2 (2.8%)	22 (3.9%)	3 (3.1%)	3 (1.2%)	4 (1.2%)
Treatment-Related SAE	0	2 (0.4%)	0	0	2 (0.6%)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.2%)	9 (1.6%)	0	29 (11.9%)	8 (2.4%)
AE Leading to Permanent Discontinuation from SOF/SOF Placebo	3 (4.2%)	8 (1.4%)	0	N/A	5 (1.5%)
AE Leading to Modification or Interruption of Study Drug	0	63 (11.1%)	7 (7.1%)	65 (26.7%)	109 (33.3%)
Death	0	1 (0.2%)	0	0	0

Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) + 30 days.

Note: Percentages were calculated based on the number of subjects in the safety analysis set.

2.2.1.3.3 Frequent Adverse Events

Table 2-3 presents AEs that were reported in $\geq 10\%$ of subjects in any treatment group across the 4 pivotal Phase 3 studies.

Table 2-3: Adverse Events in ≥10% of Subjects in Any Group by Preferred Term in the Pivotal Phase 3 Studies (Safety Analysis Set)

Preferred Term	GS-US-334-0107 (POSITRON)	P7977-1231 (FISSION) GS-US-334-0107 (POSITRON) GS-US-334-0108 (FUSION)	GS-US-334-0108 (FUSION)	P7977-1231 (FISSION)	GS-US-334-0110 (NEUTRINO)
	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any AE:	55 (77.5%)	496 (87.6%)	86 (87.8%)	233 (95.9%)	310 (94.8%)
Fatigue	17 (23.9%)	229 (40.5%)	46 (46.9%)	134 (55.1%)	192 (58.7%)
Headache	14 (19.7%)	132 (23.3%)	32 (32.7%)	108 (44.4%)	118 (36.1%)
Nausea	13 (18.3%)	114 (20.1%)	20 (20.4%)	70 (28.8%)	112 (34.3%)
Insomnia	3 (4.2%)	91 (16.1%)	28 (28.6%)	70 (28.8%)	81 (24.8%)
Rash	6 (8.5%)	48 (8.5%)	12 (12.2%)	43 (17.7%)	59 (18.0%)
Pruritus	6 (8.5%)	53 (9.4%)	7 (7.1%)	42 (17.3%)	54 (16.5%)
Decreased Appetite	7 (9.9%)	33 (5.8%)	5 (5.1%)	44 (18.1%)	58 (17.7%)
Irritability	1 (1.4%)	58 (10.2%)	11 (11.2%)	40 (16.5%)	42 (12.8%)
Diarrhea	4 (5.6%)	57 (10.1%)	6 (6.1%)	42 (17.3%)	38 (11.6%)
Dizziness	5 (7.0%)	52 (9.2%)	5 (5.1%)	33 (13.6%)	41 (12.5%)
Arthralgia	1 (1.4%)	42 (7.4%)	9 (9.2%)	35 (14.4%)	47 (14.4%)
Anemia	0	58 (10.2%)	4 (4.1%)	28 (11.5%)	68 (20.8%)
Myalgia	0	35 (6.2%)	9 (9.2%)	40 (16.5%)	45 (13.8%)
Influenza Like Illness	2 (2.8%)	16 (2.8%)	3 (3.1%)	44 (18.1%)	51 (15.6%)
Cough	2 (2.8%)	39 (6.9%)	13 (13.3%)	21 (8.6%)	34 (10.4%)
Chills	1 (1.4%)	16 (2.8%)	0	43 (17.7%)	54 (16.5%)
Vomiting	5 (7.0%)	33 (5.8%)	4 (4.1%)	23 (9.5%)	39 (11.9%)
Pyrexia	0	19 (3.4%)	3 (3.1%)	33 (13.6%)	58 (17.7%)
Depression	1 (1.4%)	34 (6.0%)	6 (6.1%)	34 (14.0%)	31 (9.5%)
Dyspnea	1 (1.4%)	45 (8.0%)	5 (5.1%)	20 (8.2%)	39 (11.9%)
Pain	2 (2.8%)	17 (3.0%)	5 (5.1%)	30 (12.3%)	33 (10.1%)
Neutropenia	0	0	0	30 (12.3%)	54 (16.5%)

Note: Adverse events are mapped according to MedDRA Version 15.0.

Note: Subjects are counted once for each system organ class (SOC), and once for each AE preferred term (PT).

Note: Data included to last dose date of study regimen (or active treatment in GS-US-334-0108) + 30 days.

2.2.1.3.4 Frequent Adverse Events During SOF+RBV Treatment

The most frequently reported AEs in **participants** in the SOF+RBV 12 and 16 Week groups were fatigue (40.5%, 229 **participants** and 46.9%, 46 **participants**, respectively), headache (23.3%, 132 **participants** and 32.7%, 32 **participants**, respectively), insomnia (16.1%, 91 **participants** and 28.6%, 28 **participants**, respectively), and nausea (20.1%, 114 **participants** and 20.4%, 20 **participants**, respectively). Fatigue and nausea were reported at a comparable incidence in **participants** in the SOF+RBV 12 and 16 Week groups. The higher incidences of headache and insomnia in the 16-Week group were unlikely due to the longer treatment duration because beginning on or after Day 84 (ie, Week 12), there were only 3 AEs of headache and no AEs of insomnia in this group.

Similar percentages of **participants** in the SOF+RBV 12 and 16-Week group experienced most of the AEs that occurred in $\geq 10\%$ of **participants**. A higher incidence of cough was reported in the SOF+RBV 16-Week group compared with the 12-Week group (13.3%, 13 **participants** and 6.9%, 39 **participants**, respectively). The higher incidence of cough in the SOF+RBV 16-Week group was unlikely due to longer treatment duration because only 2 AEs of cough began on or after Day 84 (Week 12).

The overall incidence of AEs was generally lower in the placebo group compared with the SOF+RBV 12-Week or 16-Week groups. Notably higher percentages of **participants** in the SOF+RBV 12 and 16 Week groups experienced AEs of fatigue, insomnia, anemia, dyspnea, irritability, cough, arthralgia, myalgia, and depression compared with the placebo group.

With the exception of arthralgia, each of these AEs have been previously observed with RBV treatment. [Dusheiko, 1996; McHutchison, 1998; Di Bisceglie, 1995; Brok, 2010; COPEGUS PI, 2013]. Cough has been reported when RBV was added to an HCV-treatment regimen, which may account for the increase in incidence of this AE in the SOF+RBV groups compared with placebo [Dusheiko, 1996; McHutchison, 1998].

In general, the overall incidence of AEs was highest in the PEG+RBV group compared with the placebo, SOF+RBV 12-Week, and SOF+RBV 16-Week groups. Most of the common

AEs reported in $\geq 10\%$ of **participants** in the PEG+RBV group were reported for a smaller proportion of **participants** in the SOF+RBV 12-Week and 16-Week groups. These AEs included headache, nausea, rash, pruritus, decreased appetite, irritability, diarrhea, myalgia, dizziness, influenza-like illness, arthralgia, chills, depression, pyrexia, pain, and neutropenia; all of which have been reported previously with PEG+RBV treatment [PEGASYS PI, 2011; Dusheiko, 1996].

The incidence of fatigue, headache, and nausea was highest in the PEG-containing groups (PEG+RBV or SOF+PEG+RBV), which was consistent with the expected safety profile of PEG+RBV treatment [PEGASYS PI, 2011; Ribasphere PI, 2012]. The incidence of these AEs in the placebo group (18–24%) as well as the comparable incidence of rash, pruritus, decreased appetite, dizziness, and diarrhea between the placebo, SOF+RBV 12-Week, and SOF+RBV 16-Week groups, may also suggest a relatively high background rate of these AEs in HCV-infected **participants**.

As would be expected with the administration of RBV, anemia was more commonly observed in the SOF+RBV groups than in the placebo group. Although the incidence of anemia was higher in the SOF+RBV 12-Week group than in the SOF+RBV 16-Week group (10.2%, 58 **participants** and 4.1%, 4 **participants**, respectively), the rates of Grade 2-4 anemia AEs were similar in both treatment groups (4.8%, 27 **participants** and 3.1%, 3 **participants**, respectively). Furthermore, the mean reduction in hemoglobin at the end of treatment was similar in both treatment groups (-2.1 g/dL and -2.0 g/dL, respectively).

The incidence of anemia AEs in the SOF+RBV groups was comparable to that observed in the PEG+RBV group (11.5%, 28 **participants**) where the bone marrow suppressive effects of PEG offset the lower dose of RBV used in this regimen (800 mg). Anemia was managed through dose reductions as specified in the RBV labeling and study protocols, with $< 1\%$ of **participants** receiving transfusion or erythropoietin.

2.2.1.3.5 Serious Adverse Events During SOF+RBV Treatment

Few **participants** ($\leq 4\%$) in all treatment groups in the 4 pivotal Phase 3 studies experienced an SAE.

The incidence of SAEs was comparable between the SOF+RBV 12-Week and 16-Week groups (3.9%, 22 **participants** and 3.1%, 3 **participants**, respectively. Malignant hepatic neoplasm (0.5%, 3 **participants**) and pyrexia and cellulitis (each 0.4%, 2 **participants**) were the only SAEs reported in ≥ 2 **participants** in the SOF+RBV 12-Week group. The reporting of hepatic neoplasm was not unexpected given that hepatocellular carcinoma (HCC) is a complication of cirrhosis [Naggie, 2010]. **Participants** 1055-7271 and 5586-1449, who developed malignant hepatic neoplasm, had cirrhosis in Studies GS-US-334-0107 and GS-US-334-0108, respectively. In Study GS-US-334-0108, **Participant** 1071-1492 who also developed malignant hepatic neoplasm, did not have cirrhosis based on the screening biopsy (score of F3), but this may have been unrepresentative sampling as a computer tomography scan done as part of this **participant's** evaluation for HCC reported "Cirrhotic configuration of the liver with nodular contour irregularity."

No other individual SAEs in the SOF+RBV 12-Week group were reported in >1 **participant**, and there was no apparent clustering of SAEs observed within SOC that had ≥ 5 **participants** reporting SAEs. There was no apparent trend in the types of events reported or onset time observed. For the SOF+RBV 16-Week group, no individual SAE was reported by >1 **participants**.

Treatment-related SAEs were reported in 2 **participants** (0.4%) in the SOF+RBV 12-Week group: anemia on Day 20 in **Participant** 1073-310378 and peripheral edema and eczema on post-treatment Day 28 in **Participant** 2074-7398 in Studies GS-US-334-0107 and GS-US-334-0108, respectively.

Few **participants** experienced SAEs in the placebo (2.8%, 2 **participants**) and PEG+RBV (1.2%, 3 **participants**) groups. No **participants** in these groups experienced a treatment-related SAE.

Although the rates of SAEs were higher in the SOF+RBV 12-Week and 16-Week groups (3.9%, 22 **participants** and 3.1%, 3 **participants**, respectively) than in other groups, the small difference was not considered to be clinically meaningful based on a review of the events. Furthermore, the incidence of SAEs was very low in the SOF+PEG+RBV group (1.2%, 4 **participants**).

2.2.1.3.6 Deaths During SOF+RBV Treatment

One death occurred among the 566 **participants** in the SOF+RBV 12-Week group. **Participant** 1276-310535 in Study P7977-1231 died due to cocaine and heroin intoxication (preferred term of “toxicity to various agents”) on Study Day 1. The **participant** was a 52-year-old white (Hispanic) male with a history of intravenous drug use and bipolar disorder. The death occurred on Study Day 1 and was considered unlikely to be related to study treatment. It is unknown whether the **participant** took any dose(s) of study drug because he was not observed taking his first dose in the study clinic, and study drugs were never recovered.

Three nontreatment-emergent deaths occurred (during the study follow-up period but >30 days after last dose of study drug). In Study P7977-1231, **Participant** 1225-310184 in the PEG+RBV group died due to a brain neoplasm on post treatment Day 62 which started 41 days after study drug discontinuation. In Study GS-US-334-0107, **Participant** 2074-7350 in 41 days after study drug discontinuation. In Study GS-US-334-0107, **Participant** 2074-7350 in the SOF+RBV group died of cardiogenic shock secondary to aortic stenosis 47 days after the last dose of study drug and **Participant** 5586-7322 in the SOF+RBV group died due to metastatic lung cancer 63 days after the last dose of study drug. None of the 3 nontreatment-emergent deaths was considered related to the study treatment.

2.2.1.3.7 Discontinuation of Treatment Regimen or Study Drug Dose Modification or Interruption Due to Adverse Events

Adverse events that led to discontinuation, modification, or interruption of any treatment regimen for **participants** in the 4 pivotal Phase 3 studies are described in this section.

Table 2-4 summarizes AEs that led to permanent discontinuation from any study drug in a SOF-containing treatment regimen in the 4 pivotal Phase 3 studies. Anemia was the only AE reported by more than 1 **participant** treated with a SOF-containing regimen that led to discontinuation from treatment (SOF+RBV: n=1 [0.2%], SOF+PEG+RBV: n=2 [0.6%]). The anemia event in the **participant** receiving SOF+RBV led to discontinuation of RBV; the anemia events in the 2 **participants** receiving SOF+PEG+RBV led to discontinuation of all 3 study drugs. None of the 3 events of anemia were considered serious.

Table 2-4: Adverse Events Leading to Permanent Discontinuation from any Study Drug in a SOF-Containing Treatment Regimen Reported in ≥ 2 Subjects in the Pivotal Phase 3 Studies (Screened Subjects)

	GS-US-334-0107 (POSITRON)	P7977-1231 (FISSION) GS-US-334-0107 (POSITRON) GS-US-334-0108 (FUSION)	GS-US-334-0108 (FUSION)	P7977-1231 (FISSION)	GS-US-334-0110 (NEUTRINO)
	Placebo 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+RBV 24 Weeks	SOF+PEG+RBV 12 Weeks
	(N = 71)	(N = 566)	(N = 98)	(N = 243)	(N = 327)
Number (%) of Subjects Experiencing Any AE Leading to Permanent Discontinuation from Any Study Treatment	3 (4.2%)	8 (1.4%)	0	26 (10.7%)	5 (1.5%)
Anemia	0	1 (0.2%)	0	2 (0.8%)	2 (0.6%)

Note: Adverse events are mapped according to MedDRA Version 15.0.

Note: Subjects are counted once for each system organ class (SOC), and once for each AE preferred term (PT).

2.2.1.3.8 Discontinuation of Treatment Regimen or Study Drug Dose Modification or Interruption Due to Adverse Events During SOF+RBV Treatment

The lowest rates of discontinuation of SOF+RBV due to AEs were observed in the SOF+RBV 12-Week group (1.4%, 8 **participants**) and SOF+RBV 16-Week group (0 **participants**). In the SOF+RBV groups, there were no AEs leading to permanent discontinuation of SOF+RBV that occurred in more than 1 **participant**.

In the placebo group, 3 **participants** (4.2%) had an AE that led to discontinuation of treatment regimen. The PEG+RBV group had the highest proportion of **participants** who had an AE that led to discontinuation from PEG+RBV (10.7%, 26 **participants**), compared with all other groups (0–4.2%).

Dose modification or interruption was allowed per study protocol for RBV or RBV placebo only; no dose modification of SOF was permitted. Anemia was the most commonly reported AE that led to study drug interruption or dose modification in the SOF+RBV 12-Week and 16-Week groups

(6.5%, 37 **participants** and 3.1%, 3 **participants**, respectively).

Approximately a quarter (26.7%) of **participants** in the PEG+RBV group had an AE that led to study drug interruption or dose modification. The most commonly reported AEs that led to study drug interruption or dose modification were anemia, neutropenia (each 7.8%, 19 **participants**), and thrombocytopenia (5.3%, 13 **participants**).

2.2.1.3.9 Clinical Safety Conclusions

Across clinical studies, SOF+PEG+RBV and SOF+RBV regimens were generally safe and well tolerated. Other than the expected AEs and laboratory abnormalities associated with RBV, the SOF+RBV for up to 16 weeks had a safety profile similar to that of placebo. Most AEs were mild to moderate. Severe and serious AEs were uncommon with SOF-based treatment and there were no consistent trends in type or timing of these events other than what would be expected with RBV with or without PEG.

Across all groups in the pivotal Phase 3 studies (SOF+RBV 12-Week, SOF+RBV 16-Week, SOF+PEG+RBV, PEG+RBV, and placebo), the 3 most frequently occurring AEs were fatigue, headache, and nausea. The incidence of these events was highest in the PEG-containing groups (PEG+RBV or SOF+PEG+RBV), which was consistent with the expected safety profile of PEG+RBV treatment [PEGASYS PI, 2011; Ribasphere PI, 2012]. Other than the expected AEs and laboratory abnormalities associated with RBV, the SOF+RBV 12 and 16 Week groups had a safety profile similar to the placebo group. No additional AEs than those in the expected safety profile for PEG+RBV or RBV were identified in the SOF+RBV or SOF+PEG+RBV groups.

2.2.2 Ribavirin (RBV)

RBV is a guanosine analogue that inhibits the in vitro replication of a wide range of RNA and DNA viruses [COPEGUS, Jan 2010 and March 2010]. RBV monotherapy has little or no effect on the replication of HCV but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy [Poynard, 1998; McHutchison, 1998].

RBV is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in

semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. A comprehensive review of RBV is contained in the package insert/SmPC.

2.2.3. Ledipasvir/sofosbuvir (LDV/SOF)

LDV/SOF is an all-oral, once daily treatment regimen for chronic HCV infection. As such, it obviates the toxicity and tolerability issues, as well as the contraindications, associated with Peg-IFN and/or RBV. As of 21 March 2014, 23 clinical studies have been initiated with LDV/SOF alone or in combination with RBV, including 344 healthy participants and 3504 participants with chronic HCV infection.

2.2.3.1 Clinical Efficacy in Participants with Genotype 1 HCV infection and HIV Co-infection

The efficacy data for LDV/SOF in Genotype 1 and 4 HCV infection is derived from the Phase 3 ION-4 study, which was a multicenter, open-label, single arm study of LDV/SOF for 12 weeks. The trial included HCV treatment-naïve and treatment-experienced (55%) participants and included 20% of participants with cirrhosis. Participants were required to be on ARVs and have evidence of HIV viral suppression. The allowable ARVs included tenofovir disoproxil fumarate (TDF) plus EFV, raltegravir (RAL), or rilpivirine (RPV). Overall the study population was 82% male, 34% self-reported black race, 24% IL28B CC genotype, and 98% GT1 (75% 1a, 23% 1b, 8 genotype 4). The overall SVR12 was 96% (96% GT1 and 100% GT4). Virologic failures included 10 participants with relapse after end of therapy and 2 participants with breakthrough due to nonadherence. One participant was lost to follow-up after achieving SVR4 although this participant did return for SVR24 visit. There was one death for an unrelated event (infectious endocarditis in IDU). There was no difference in SVR12 for treatment-naïve (95%), treatment-experienced (97%), cirrhosis (94%), no cirrhosis (96%), treatment-experienced with cirrhosis (98%). In a multivariable analysis only self-reported black race was associated with a lower SVR12 (90%). This association of lower SVR12 and race was not observed in the mono-infected Phase 3 program. Further investigations to explain this observation in ION-4, including population PK across race, ARV regimen, relapse and a candidate gene study of the CYP2B6 polymorphism, were negative. Deep sequencing was completed on all participants and NS5A resistant variants (RAV) were identified at baseline in 20% of participants; this did not associate with lower SVR12 (94% with RAVs at baseline vs 96% without). Ten of the 12 virologic failures in the study had RAV at failure, 4 of these were relapsers who had the RAVs at baseline.

2.2.3.2 Clinical Efficacy in HCV Mono-infection

The primary efficacy data for LDV/SOF in genotype 1 HCV infection in the clinical efficacy section is derived from 3 Phase 3 ION studies (GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], and GS-US-337-0108 [ION-3]). Studies GS-US-337-0102 and GS-US-337-0109 evaluated treatment with LDV/SOF±RBV for 12 or 24 weeks in treatment-naïve and treatment-experienced participants, respectively, who were infected with genotype 1 HCV. Both studies enrolled up to 20% of HCV-infected participants who had documented compensated cirrhosis. Study GS-US-337-0108 evaluated LDV/SOF±RBV treatment for 8 weeks and LDV/SOF treatment for 12 weeks in noncirrhotic treatment-naïve participants with genotype 1 HCV infection [Harvoni PI, 2015].

Additional data from Phase 2 studies that provide clinical efficacy information for retreatment of virologic failures to prior SOF-based regimens (Studies 13-I-0066 [SYNERGY] and GS-US-337-0118 [LONESTAR]) are also presented.

Efficacy data across the Phase 3 ION studies were not pooled or grouped with the exception of those for noncirrhotic treatment-naïve participants from the LDV/SOF 12-week groups in Studies GS-US-337-0102 and GS-US-337-0108. These 2 studies had data for LDV/SOF 12-week groups pooled for purposes of subgroup analysis of noncirrhotic treatment-naïve participants. With the exception of this 1 subset of participants, different participant populations were enrolled in each study.

2.2.3.2.1 Participant Disposition

Of the 1952 participants who received at least 1 dose of study drug in the LDV/SOF Phase 3 ION studies, 98.1% completed their assigned study treatment, and 0.7% of participants discontinued study treatment due to an AE. Two participants discontinued treatment due to lack of efficacy, and, in both cases, PK data suggested study drug noncompliance (Studies GS-US-337-0102 and GS-US-337-0109).

2.2.3.2.2 Demographics and Baseline Disease Characteristics

Overall, demographic characteristics were generally similar across all treatment groups in the LDV/SOF Phase 3 ION population; however, because Study GS-US-337-0102 enrolled 40.8% of participants in Europe, notable differences in demographics between the US and Europe compared with groups in Studies GS-US-

337-0109 and GS-US-337-0108 were observed for race and BMI as follows: in the US, a higher percentage of participants were black or African-American (19.5% US vs. 2.3% Europe) and had a BMI ≥ 30 kg/m² (27.3% US vs. 9.3% Europe). Overall, baseline disease characteristics were generally similar across all treatment groups. A total of 11.5% of participants had cirrhosis at screening: 15.7% and 20.0% of participants had cirrhosis at screening in Studies GS-US-337-0102 and GS-US-337-0109, respectively. No participants had cirrhosis at screening in Study GS-US-337-0108. The majority of participants had genotype 1a (73.9%) or 1b (25.5%) HCV infection; 5 participants had genotype 1 (no subtype per the protocol-specified clinical assays) HCV infection, 2 participants had genotype 4 HCV infection, and 5 participants had no genotype determined by the protocol-specified clinical assays. The 7 participants who had either genotype 4 HCV infection or no genotype determined for their HCV infection were randomized in violation of the clinical study protocols [Harvoni PI, 2015].

2.2.3.2.3 Study GS-US-337-0102 (ION-1): Treatment-Naive Participants

In Study GS-US-337-0102, both 12-week groups met the primary efficacy endpoint of an SVR12 rate that was superior to the historical control rate of 60% ($p < 0.001$) and the prespecified interim criteria of SVR12 $\geq 90\%$ in participants with and without cirrhosis separately. The SVR12 rates were 97.7% for the LDV/SOF 12-week group and 97.2% for the LDV/SOF+RBV 12-week group.

Participants with and without cirrhosis achieved high rates of SVR12: SVR12 rates in participants with cirrhosis were 94.1% in the LDV/SOF 12-week group and 100% in the LDV/SOF+RBV 12-week group; SVR12 rates in participants without cirrhosis were 98.3% in the LDV/SOF 12-week group and 96.7% in the LDV/SOF+RBV 12-week group.

In the LDV/SOF 12-week group, only 1 participant relapsed and 4 participants did not have a post treatment Week 12 visit and were classified as failures. The participant who relapsed had IL28B TT alleles, cirrhosis, and the baseline NS5A resistance-associated variant (RAVs) L31M, and relapsed at the post treatment Week 4 visit; the participant had completed 12 weeks of

LDV/SOF without any dose interruptions. In the LDV/SOF+RBV 12-week group, no participants relapsed and 6 participants did not have a post treatment Week 12 visit and were classified as failures. Across all 4 treatment groups, 1 participant in the LDV/SOF 24-week group had on-treatment virologic failure at Week 8 (breakthrough), associated with documented study drug noncompliance.

Several host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no notable impact on SVR12 rates. The presence of baseline LDV-associated NS5A RAVs in 78 participants also had no notable impact on SVR12 rates.

2.2.3.2.4 Study GS-US-337-0108 (ION-3): Treatment-Naive Participants

All treatment groups met the primary efficacy endpoint of an SVR12 rate that was statistically significantly higher ($p < 0.001$) than the adjusted historical SVR null rate of 60%. The SVR12 rates were 94.0% for the LDV/SOF 8-week group, 93.1% for the LDV/SOF+RBV 8-week group, and 95.4% for the LDV/SOF 12-week group.

The 8-week, RBV-free LDV/SOF regimen was noninferior to the 8-week RBV-containing regimen and the 12-week LDV/SOF regimen, as demonstrated by lower bound 95.0% CI of -3.9% and lower bound 97.5% CI of -6.4%, respectively, based on the requirement that the lower bound of the CI of the difference between two treatment groups was greater than the prespecified noninferiority margin of -12%.

The addition of RBV to an 8-week treatment course of LDV/SOF or extension of the LDV/SOF treatment duration from 8 to 12 weeks did not substantially increase the observed SVR12 rates. Relapse rates were similar in the 8-week treatment groups, but were lower in the LDV/SOF 12-week group.

The overall virologic failure rate was low (LDV/SOF 8 Weeks: 5.1%, LDV/SOF+RBV 8 Weeks: 4.2%, and LDV/SOF 12 Weeks: 1.4%). No resistance to SOF or LDV was detected in 21 and 7 of the 23 relapsed participants, respectively. Virologic failure was associated with

single-class LDV resistance in 16 (69.6%) of the relapse participants. The substitutions V321A and L159F in NS5B were each detected in 1 participant with genotype 1a HCV infection at low levels at relapse. E237G, a conserved site substitution in NS5B, but distant from the active site, was detected in 2 genotype 1a participants at virologic failure. Eleven participants who achieved SVR4 did not achieve SVR12: 5 participants in the LDV/SOF 8-week group (3 relapsed, 1 lost to follow-up, and 1 withdrew consent); 4 participants in the LDV/SOF+RBV 8-week group (3 relapsed, 1 lost to follow-up) and 2 participants in the LDV/SOF 12-week group (2 participants had visits that had not occurred at time of data cut and were considered lost to followup).

Prespecified analyses of subgroups indicated that the SVR12 rates across the 3 treatment groups were generally consistent with those observed in the overall population, with high SVR12 rates observed in most subgroups.

For the 8-week treatment groups, exact univariate logistic regression analysis was used to assess the relationship between relapse and 10 prognostic factors (treatment with vs. without RBV, age, sex, race, ethnicity, HCV genotype 1 subtype, baseline HCV RNA viral load, BMI, IL28B alleles, and gamma-glutamyl transferase [GGT]). Among the 10 factors included in the analysis, 2 were found to be significant ($p < 0.05$). These were male sex and having a baseline HCV RNA viral load $\geq 800,000$ IU/mL. Of note, the analysis showed that the absence of RBV in an 8-week regimen consisting of LDV/SOF was not a significant predictor of relapse. Additionally, several other host and viral factors that have traditionally been predictive of, or associated with, relapse (eg, age > 65 years, black or African-American, Hispanic or Latino, high BMI, non-CC IL28B alleles) were not found to be significant in this analysis. Subsequent exact multivariate regression analysis identified only 1 factor, male sex, to be the most predictive of relapse, among the limited number of participants who relapsed. Although the SVR12 rate was numerically lower among male participants than female participants, the majority of male participants (92.6%, 225 of 243 participants) and female participants (98.9%, 178 of 180 participants) achieved SVR12 after 8 weeks of therapy.

	ION-3	ION-3	ION-3	ION-1	ION-1
	LDV/SOF 8-Week N=215 (%)	LDV/SOF+ RBV 8-Week N=216 (%)	LDV/SOF 12-Week N=216 (%)	LDV/SOF 12-Week N=214 (%)	LDV/SOF+ RBV 12-Week N=217 (%)
Treatment-Naïve Total					
SVR12	202/215 (94)	201/216 (93)	206/216 (95)	209/214 (98)	211/217 (97)
95% CI	89.9 - 96.7%	88.8 – 96.1	91.7 – 97.8	94.6 – 99.2	94.1 – 99.0
P-value*	<0.001	<0.001	<0.001	<0.001	<0.001
Treatment-Naïve Noncirrhotic					
SVR12	202/215 (94)	201/216 (93)	206/216 (95)	177/180 (98)	178/184 (97)
95% CI	89.9 – 96.7	88.8 – 96.1	91.7 – 97.8	95.2 – 99.7	93.0 – 98.8
Treatment-Naïve Cirrhotic					
SVR12	NA	NA	NA	32/34 (94)	33/33 (100)
95% CI	--	--	--	80.3 – 99.3	89.4 - 100

*Compared to historic control of 60%

2.2.3.2.5 Participants Retreated After Virologic Failure Final

Participants who have failed either a SOF-containing regimen or a LDV/SOF-containing regimen have been retreated or will be retreated with LDV/SOF±RBV in the following studies: GS-US-337-0118 (LONESTAR), GS-US-337-0122 (ELECTRON-2), GS-US-337-1118, and an ongoing non-Gilead-sponsored study (Study 13-I-0066 [SYNERGY]; IND 116585). Resistance and SVR data from 20 participants, 1 from Study GS-US-337-0118 (final data) and 19 from Study GS-US-337-0122 (preliminary data), are currently available. Of these 20 retreatment participants, 11 had relapsed after treatment with a SOF-containing regimen and 9 had relapsed after treatment with a LDV/SOF-containing regimen. To date, all participants have achieved SVR12 following retreatment.

2.2.3.2.6 Clinical Efficacy Conclusions

In the LDV/SOF Phase 3 clinical program, LDV/SOF±RBV treatment was evaluated for 12 or 24 weeks in treatment-naïve and treatment-experienced participants in Studies GS-US-337-0102 and GS-US-337-0109, respectively, with genotype 1 HCV infection. Both studies enrolled up to 20% HCV-infected participants who had documented compensated cirrhosis. Study GS-US-337-0108 evaluated LDV/SOF±RBV treatment for 8 weeks and LDV/SOF treatment for 12 weeks in noncirrhotic treatment-naïve participants with genotype 1 HCV

infection. Across all studies, LDV/SOF demonstrated a high degree of efficacy with point estimates for SVR12 >93% in participants with genotype 1 HCV infection.

Across the three Phase 3 studies, the addition of RBV to the LDV/SOF regimen did not substantially increase the SVR rate. When the SVR rates are considered, extending the duration of LDV/SOF treatment from 8 to 12 weeks in noncirrhotic treatment-naïve participants in Study GS-US-337-0108 and 12 to 24 weeks in noncirrhotic or cirrhotic treatment-experienced participants in Study GS-US-337-0109 would not enhance the observed SVR12 rates for the majority of participants. Concordance analysis between SVR12 and SVR24 in treatment-naïve and treatment-experienced participants receiving LDV/SOF for 12 or 24 weeks was 100% in the Phase 3 Studies GS-US-337-0102 and GS-US-337-0109. There was no clinically meaningful impact on SVR12 rates or relapse when participants took LDV/SOF with or without food in any study.

Comprehensive analyses showed that no genotypic or phenotypic resistance to either SOF or LDV was detected in 8 of 37 participants (22%) at virologic failure in the Phase 3 studies. Virologic failure was associated with single-class LDV phenotypic resistance in 29 of 37 participants (78%). Low levels of V321A and L159F in NS5B, 2 substitutions previously identified to be SOF treatment-emergent substitutions with no phenotypic resistance to SOF, were detected in 1 participant with genotype 1a HCV infection at relapse by deep sequencing. In addition, E237G, a conserved site substitution in NS5B, but distant from the active site, was observed in 2 participants with genotype 1a HCV infection and 1 participant with genotype 1b infection at virologic failure. The clinical significance of these NS5B substitutions is unknown. No genotypic or phenotypic resistance to SOF was detected in the remaining participants.

Overall, pre-existing baseline NS5A RAVs have a poor predictive value for virologic failure when participants are treated with a dual combination of SOF and LDV. Among all participants who had baseline NS5A RAVs, an SVR12 rate of 89.5% (34/38 participants) or 92.1% (82/89 participants) was observed among participants treated with LDV/SOF for 8 or 12 weeks, respectively. Nevertheless, among participants with baseline NS5A

RAVs, there were slight reductions in SVR12 observed, associated with NS5A RAVs expressing higher levels of LDV resistance within the treatment-experienced population. From a clinical perspective, the lack of a high predictive value between viral sequence and treatment outcome coupled with the observation that a large majority of participants with NS5A RAVs achieve SVR12 appears to preclude the clinical utility of baseline sequencing.

2.2.3.3 Clinical Safety

The primary safety data for this clinical safety section are derived from the 3 Phase 3 LDV/SOF ION studies (GS-US-337-0102 [ION-1], GS-US-337-0109 [ION-2], GS-US-337-0108 [ION-3]) with supporting safety data from other studies as appropriate. The ION-4 safety analysis confirmed the clinical safety reported in the rest of the ION program.

2.2.3.3.1 Adverse Events

Treatment-emergent AEs were any events with onset dates on or after the date of the first dose of any study drug up to 30 days after the last dose of any study drug.

2.2.3.3.2 Overall Summary of Adverse Events

Table 2-5 presents an overall summary of AEs reported in the 3 Phase 3 ION studies. Of the participants in these studies, 79.1% had at least 1 AE and 4.7% had at least 1 Grade 3 or 4 AE. In addition, 2.6% of participants had at least 1 SAE, with only 0.3% of participants experiencing a treatment-related SAE (Section 2.2.3.3.4).

Overall, <1% of participants receiving LDV/SOF with or without RBV (0.7%) had an AE leading to discontinuation of LDV/SOF. The only AEs that led to discontinuation of LDV/SOF in >1 participant were palpitations and anxiety (2 participants each) (Section 2.2.3.3.6).

A higher proportion of participants in the RBV-containing (LDV/SOF+RBV) treatment groups (13.5%) had AEs leading to dose modification or interruption of any study drug than participants in the RBV-free (LDV/SOF) treatment groups (0.6%).

No treatment-emergent deaths were reported in the three Phase 3 studies. One nontreatment-emergent death was reported in a participant who had an SAE of hepatic failure secondary to HCV infection and alcohol use on post treatment Day 38. The participant died of liver failure on post treatment Day 121 (Section 2.2.3.3.5).

The difference in the AE profile of RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) treatment groups was also evaluated. The percentage differences for the 8-, 12-, or 24-week treatment durations and overall risk differences (adjusted for treatment duration based on Mantel-Haenszel proportions) were calculated for the AE brief summary and for AEs and treatment-related AEs that occurred in at least 5% of participants within any treatment group. The addition of RBV to the treatment regimen was associated with an increase in the total incidence of AEs for all treatment durations. Overall, when adjusted for treatment duration, the addition of RBV increased the risk of a participant experiencing any AE by 11.1%, the risk of a participant experiencing any treatment-related AE by 25.7%, and the risk of a participant experiencing any AE leading to modification or interruption of any study drug by 13.0%. For Grade 3 or 4 AEs, Grade 3 or 4 treatment-related AEs, SAEs, treatment-related SAEs, AEs leading to permanent discontinuation of any study drug, AEs leading to permanent discontinuation of LDV/SOF, and AEs leading to interruption of LDV/SOF, the risk differences between the LDV/SOF and LDV/SOF+RBV treatment regimens were small (<5%). The majority of AEs attributable to the addition of RBV to LDV/SOF were Grade 1 to 2 in severity.

The ION-4 reported 77% of participants with AEs, 4% with grade 3-4 (only 4 of the 14 were reported as related to the study regimen), 8 with severe AE (including 2 diagnoses of hepatocellular carcinoma and 2 diagnoses of portal vein thrombosis). No participant discontinued treatment due to AE. Eleven percent of participants had a grade 3-4 laboratory abnormality but these were all transient and asymptomatic (elevated glucose in diabetic participants, elevated lipase and creatinine kinase). All participants maintained stable CD4 throughout the study and no participant had confirmed HIV virologic rebound. Common AEs ($\geq 5\%$) included headache (25%), fatigue (21%), diarrhea (11%), nausea

(10%), arthralgia (7%), and upper respiratory tract infection (5%). This is quite similar to Tables 2-5 and 2-6 below. Due to the drug-drug interaction of LDV and TDF leading to increased serum TFV levels all participants had close renal monitoring at all study visits. There was no clinically or statistically significant increase in serum creatinine or decrease in creatinine clearance (CrCl) during the study. Four participants met the study protocol defined criteria of confirmed, treatment-emergent, renal insufficiency (creatinine \geq 0.4 mg/dL). Two of these participants were simply monitored and in the absence of any evidence of tubular toxicity no changes were made in ARVs. One participant entered the study on RAL and had baseline CrCl of approximately 50 mL/min. With worsening CrCl but no evidence of tubular toxicity this participant had dose reduction of TDF as per package insert. The fourth participant also entered the study with evidence of chronic kidney disease (CKD) with CrCl of approximately 80 mL/min and baseline 4+ glucosuria and 2+ proteinuria. This participant had worsening renal function on study and due to the concern for tubular damage at baseline the decision was made to switch this participant off of TDF to RAL. The participant completed the study on EFV, RAL and lamivudine (3TC) without difficulty and achieved SVR12.

Table 2-5: Overall Summary of Adverse Events in LDV/SOF Phase 3 Safety Population

Number (%) of Subjects Experiencing Any:	ION-3 LDV/SOF 8 Week N=215	RBV-Free Regimens (ION-1, 2, 3) Overall (N=1080)	RBV-Containing Regimens (ION-1, 2, 3) Overall (N=872)
AE	145 (67%)	800 (74%)	745 (85%)
Grade 3 or 4 AE	2 (0.9%)	46 (4.3%)	45 (5.2%)
Treatment-Related AE	82 (38%)	484 (44.8%)	617 (70.8%)
Grade 3 or 4 Treatment-Related AE	0	11 (1.0%)	27 (3.1%)
SAE	4 (1.9%)	34 (3.1%)	17 (1.9%)
Treatment-Related SAE	0	4 (0.4%)	1 (0.1%)
AE Leading to Permanent Discontinuation of Any Study Drug	0	6 (0.6%)	11 (1.3%)
AE Leading to Permanent Discontinuation of LDV/SOF	0	6 (0.6%)	7 (0.8%)
AE Leading to Modification or Interruption of Any Study Drug	0	6 (0.6%)	118 (13.5%)
AE Leading to Interruption of LDV/SOF	0	6 (0.6%)	7 (0.8%)
Treatment-Emergent Death	0	0	0

2.2.3.3.3 Frequent Adverse Events Final

Table 2-6 presents the AEs reported for at least 5% of subjects in any treatment group by preferred term in the three Phase 3 ION studies. Overall, the 3 most frequently reported AEs were fatigue (29.3%), headache (23.1%), and nausea (13.5%). All of these events were reported more commonly in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF: fatigue (38.0% vs. 22.2%), headache (26.1% vs. 20.6%), and nausea (17.4% vs. 10.4%).

The majority of AEs reported in at least 5% of participants occurred more commonly in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF. Furthermore, irrespective of treatment duration (8 vs. 12 vs. 24 weeks), the AEs with a $\geq 5\%$ risk difference were generally similar across the 3 treatment durations (8 vs. 12 vs. 24 weeks). Therefore, a pooled analysis, which adjusted for treatment duration, was used to identify AEs occurring at $\geq 5\%$ incidence in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF. These AEs were fatigue, insomnia, anemia, nausea, dyspnea, irritability, cough, rash, pruritus, and headache. All of these events

were associated with the expected safety profile of RBV [Dusheiko, 1996; Ribasphere PI, 2012; COPEGUS PI, 2013].

When evaluated at the system-organ-class level, numerically higher percentages (difference of >5%) of participants receiving LDV/SOF+RBV than participants receiving LDV/SOF experienced AEs within the following system organ classes: blood and lymphatic system disorders (10.7% vs. 1.5%); gastrointestinal disorders (39.6% vs. 30.6%); general disorders and administration site conditions (52.5% vs. 33.8%); infections and infestations (23.7% vs. 18.4%); nervous system disorders (36.9% vs. 27.8%); psychiatric disorders (29.6% vs. 16.2%); respiratory, thoracic, and mediastinal disorders (25.2% vs. 11.5%); and skin and subcutaneous tissue disorders (29.7% vs. 14.3%). No system organ class had an incidence of AEs higher (>5%) in participants receiving LDV/SOF compared with participants receiving LDV/SOF+RBV.

Longer treatment duration (8 vs. 12 vs. 24 weeks) was associated with an increase in the total incidence of AEs, both in the LDV/SOF groups (67.4%, 72.4%, and 81.3%, respectively) and LDV/SOF+RBV groups (76.4%, 85.4%, and to 91.5%, respectively).

When comparing the LDV/SOF groups by treatment duration, the differences in the incidence of any individual AE between 8 and 12 weeks of treatment or between 12 and 24 weeks of treatment were small (<5%); headache was the only AE with increased incidence of ≥5% when the treatment durations increased from 8 to 12 weeks.

When comparing the LDV/SOF+RBV groups by treatment duration, most of the differences in the incidence of any individual AE between 8 and 12 weeks of treatment were small (<5%); insomnia, cough, asthenia, and dyspnea were exceptions with increased incidence of ≥5% when the treatment durations increased from 8 to 12 weeks. Similarly, the differences in the incidence of any individual AE between 12 and 24 weeks of treatment were small (<5%), with the exception of headache, which had an increased incidence of ≥5% when the treatment duration increased from 12 to 24 weeks.

Table 2-6: Adverse Events in at Least 5% of Subjects in Any Treatment Group by Preferred Term in the LDV/SOF Phase 3 Safety Population

	ION-3 LDV/SOF 8 Week N=215	RBV-Free Regimens (ION-1, 2, 3) Overall (N=1080)	RBV-Containing Regimens (ION-1, 2, 3) Overall (N=872)
Number (%) of Subjects Experiencing Any AE:	145 (67%)	800 (74%)	745 (85%)
Fatigue	45 (21%)	240 (22.2%)	331 (38%)
Headache	30 (14%)	222 (20.6%)	228 (26.1%)
Nausea	15 (7%)	112 (10.4%)	152 (17.4%)
Insomnia	11 (5.1%)	82 (7.6%)	155 (17.8%)
Diarrhea	15 (7%)	88 (8.1%)	67 (7.7%)
Irritability	3 (1.4%)	46 (4.3%)	95 (10.9%)
Rash	3 (1.4%)	47 (4.4%)	94 (10.8%)
Arthralgia	9 (4.2%)	68 (6.3%)	66 (7.6%)
Cough	3 (1.4%)	42 (3.9%)	90 (10.3%)
Pruritis	2 (0.9%)	33 (3.1%)	78 (8.9%)
Dizziness	6 (2.8%)	47 (4.4%)	61 (7%)
Constipation	9 (4.2%)	53 (4.9%)	42 (4.8%)
Myalgia	7 (3.3%)	47 (4.4%)	48 (5.5%)
Asthenia	1 (0.5%)	38 (3.5%)	56 (6.4%)
Anemia	2 (0.9%)	5 (0.5%)	84 (9.6%)
Muscle Spasms	3 (1.4%)	28 (2.6%)	57 (6.5%)
Back Pain	6 (2.8%)	43 (4.0%)	40 (4.6%)
Dyspnea	0	12 (1.1%)	69 (7.9%)
Anxiety	5 (2.3%)	30 (2.8%)	49 (5.6%)
Nasopharyngitis	3 (1.4%)	38 (3.5%)	41 (4.7%)
Vomiting	6 (2.8%)	24 (2.2%)	40 (4.6%)
Dry Skin	1 (0.5%)	10 (0.9%)	43 (4.9%)
Dyspnea Exertional	0	6 (0.6%)	35 (4%)

2.2.3.3.4 Serious Adverse Events in Phase 3 ION Studies

Overall in the Phase 3 ION studies (GS-US-337-0102, GS-US-337-0109, and GS-US-337-0108), few participants (2.6%, 51 of 1952 participants) had any SAE. The only SAEs reported in >1 participant across all treatment groups were noncardiac chest pain (3 participants), and chest pain, colitis, gastroenteritis, hand fracture, hypertension, intervertebral disc protrusion, and pneumonia (2 participants each), suggesting that no trends in SAE type or onset time were observed. Only 5

participants (0.3%) had an SAE that was considered related to study drug by the investigator: anemia, development of factor VIII inhibitor, mesenteric vein thrombosis, salpingitis, and headache. These events are described below:

1. A participant in the LDV/SOF+RBV 12-week group had 2 separate treatment-related SAEs of anemia; both events were Grade 3, led to interruption of the RBV dose, and resolved.
2. A participant with cirrhosis in the LDV/SOF 24-week group had a treatment-related SAE of mesenteric vein thrombosis; this event was Grade 3, led to the interruption of the LDV/SOF dose, and resolved.
3. A participant with a medical history of hemophilia A in the LDV/SOF 24-week group, who had received factor VIII supplementation prior to and during the study, had a treatment-related SAE of development of factor VIII inhibitor; this event was Grade 3, led to the discontinuation of LDV/SOF, and was ongoing at the time of the data cut.
4. A participant in the LDV/SOF 24-week group had a treatment-related SAE of salpingitis; this event was Grade 3, did not lead to a dose change for LDV/SOF, and resolved.
5. A participant in the LDV/SOF 24-week group had a treatment-related SAE of headache; this event was Grade 3, occurred on post treatment Day 6, and was ongoing at the time of the data cut.

2.2.3.3.5 Deaths: Participants in Phase 3 ION Studies

One treatment-emergent death was reported in the LDV/SOF Phase 3 Safety Population. This participant was in the ION-4 trial and was discontinued from the study at week 4 due to hospitalization for severe staphylococcal aureus infective endocarditis resulting in multi-organ failure and death in a participant actively using intravenous drugs.

One nontreatment-emergent death was reported in Study GS-US-337-0102. This participant, who had received LDV/SOF for 12 weeks and achieved SVR12, was reported to have died of hepatic failure on post treatment Day 121. This participant had an SAE of hepatic failure secondary to HCV infection and alcohol

use on post treatment Day 38; this event was considered not related to study drug by the investigator.

2.2.3.3.6 Discontinuations Due To Adverse Events: Participants in Phase 3 ION Studies

Overall, the incidence of AEs leading to permanent discontinuation of any study drug was low across all treatment groups (0.9%, 17 of 1952 participants). Anemia, anxiety, fatigue, and rash were the only AEs leading to permanent discontinuation of any study drug in >1 participant (2 participants each); these were reported in the LDV/SOF+RBV treatment groups and are consistent with the expected safety profile of RBV [Dusheiko, 1996; Ribasphere PI, 2012; COPEGUS PI, 2013].

All participants who discontinued LDV/SOF were required to discontinue the entire study treatment regimen (ie, for the RBV-containing [LDV/SOF+RBV] groups, RBV was also discontinued). Across treatment groups, palpitations and anxiety were the only AEs leading to discontinuation of LDV/SOF reported in >1 participant (2 participants each). All of these events were Grade 1 or 2 in severity and resolved following the discontinuation of LDV/SOF.

2.2.3.3.7 Clinical Safety Conclusions

The LDV/SOF Phase 3 clinical program compared the safety and tolerability of LDV/SOF with and without RBV for treatment durations of 8, 12, and 24 weeks. A total of 1952 participants received at least 1 dose of study drug and 98.1% of these participants completed their assigned study treatment.

Across the LDV/SOF Phase 3 Safety Population, treatment with LDV/SOF was generally safe and well tolerated. The incidence of AEs leading to permanent discontinuation of any study drug was low (0.9%) across all regimens, with no AEs leading to permanent discontinuation of any study drug that occurred in >1 participant in the LDV/SOF treatment groups; the only AEs leading to permanent discontinuation of any study drug in >1 participant in the LDV/SOF+RBV treatment groups included AEs consistent with the expected safety profile of RBV (anemia, anxiety, fatigue, and rash [2 participants each]) [Dusheiko, 1996; Ribasphere PI,

2012; COPEGUS PI, 2013]. Across the LDV/SOF Phase 3 Safety Population, the 3 most frequently occurring AEs were fatigue, headache, and nausea. A higher incidence of each event was reported in participants receiving LDV/SOF+RBV compared with participants receiving LDV/SOF: fatigue (38.0% vs. 22.2%), headache (26.1% vs. 20.6%), and nausea (17.4% vs. 10.4%).

The addition of RBV to LDV/SOF increased the number of AEs experienced by participants. Overall, AEs were 11.1% and treatment-related AEs were 25.7% more likely to occur in the RBV-containing (LDV/SOF+RBV) groups compared with the RBV-free (LDV/SOF) groups. In addition, the need for study drug modification or dose interruption due to any AE was 13.0% more frequent in the RBV-containing (LDV/SOF+RBV) groups compared with the RBV-free (LDV/SOF) groups. The specific AEs that increased in the presence of RBV were fatigue, insomnia, anemia, nausea, dyspnea, irritability, cough, rash, pruritus, and headache.

For both RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) regimens, increasing treatment duration from 8 to 12 weeks and from 12 to 24 weeks resulted in small but consistent increases in the incidence of AEs, but did not change the observed AE profile.

No treatment-emergent deaths were reported in the LDV/SOF Phase 3 Safety Population and few participants (2.6%) had any SAE. The only SAEs reported in >1 participant across all treatment groups were noncardiac chest pain (3 participants), and chest pain, colitis, gastroenteritis, hand fracture, hypertension, intervertebral disc protrusion, and pneumonia (2 participants each), suggesting that no trends in SAE type or onset time were observed. Only 5 participants (0.3%) had an SAE that was considered related to study drug by the investigator.

Grade 4 laboratory abnormalities were reported in only 1.0% of participants for both the RBV-free (LDV/SOF) and RBV-containing (LDV/SOF+RBV) groups. Grade 3 laboratory abnormalities were reported in 5.4% of participants in the RBV-free (LDV/SOF) groups and 11.4% of participants in the RBV-containing (LDV/SOF+RBV) groups. The increased incidence of Grade 3 laboratory abnormalities in the RBV-containing

(LDV/SOF+RBV) groups compared with Grade 3 laboratory abnormalities in the RBV-free (LDV/SOF) groups was driven largely by hemoglobin abnormalities. The addition of RBV to a LDV/SOF treatment regimen contributed substantially to the incidence of anemia that required dose modification or discontinuation (hemoglobin <10 g/dL). A small number of participants with changes in non-hematologic laboratory parameters met the criteria for Grade 3 and 4 laboratory abnormalities. The most common Grade 3 or 4 chemistry laboratory abnormalities across all treatment groups were increased lipase (1.7%) and increased serum glucose (1.5%). In participants with Grade 3 or 4 increased lipase, no case of Grade 3 or 4 increased lipase was associated with clinical signs or symptoms of pancreatitis. Only 1 case of pancreatitis occurred in the entire Phase 3 program; this event occurred post treatment in a participant with a history of chronic pancreatitis and was not associated with a Grade 3 or 4 increased lipase. Among participants who experienced a Grade 3 or 4 increased serum glucose, all participants had a history of diabetes, were taking diabetes medication, or had glucose intolerance (denoted by HbA1c >6.0% at screening).

2.3 Rationale for Inclusion of Concomitant ARV Regimens

SOF is a uridine nucleotide analogue. Nucleo(s)ide analogues have a low potential for drug interactions because they are primarily renally eliminated and not substrates, inhibitors, or inducers of the cytochrome P450 enzyme system. SOF has been coadministered with multiple ARVs (EFV/emtricitabine [FTC]/ TDF, **atazanavir boosted with ritonavir [ATV/r]**, **darunavir boosted with ritonavir [DRV/r]**, RAL or RPV) without evidence of clinically significant drug interactions [Sovaldi PI, 2015]. **LDV has some interactions with antiretroviral agents. In healthy volunteers, TFV is increased 40% with FTC/RPV/TDF and 98% with EFV/FTC/TDF following administration of LDV/SOF (Study GS-US-337-0127). A reduction in LDV exposure of approximately 34% was observed with EFV/FTC/TDF. The ION-4 included EFV, RAL, or RPV in combination with TDF/FTC without evidence of clinically significant drug interactions. In fact in the ION-4 the mean TFV exposure (AUC_{tau}) was lowest in participants on EFV (3600 ng*h/mL) and greatest in participants on RPV (4286 ng*h/mL) and the overall mean TFV exposure was lower in the ION-4 population (3838 ng*h/mL) than in the healthy volunteer population (~4500 ng*h/mL). In addition, LDV levels were not different across the ARV regimens in the ION-4, unlike in the healthy volunteer studies [Naggie, CROI 2015 abstract LB152]. TFV is increased with the addition of LDV/SOF in the setting of boosted HIV protease inhibitors (PIs), ATV/r and DRV/r. TFV concentrations are increased 30-60% with the addition of LDV/SOF compared to the concentrations of TFV observed in participants taking ATV/r or DRV/r with TDF/FTC [German, CROI 2015**

abstract 82]. The mechanism and clinical significance of the interaction is currently unknown, but additional monitoring for potential renal toxicity is warranted [Recommendations for Testing, Managing, and Treating Hepatitis C, 2014] and will be performed in this study in participants taking this combination. Cobicistat (COBI) C_{min} is increased 1.25-4.25 fold by LDV; however, the AUC change is 1.59 fold, which is not felt to be clinically meaningful. The package insert for the approval of LDV/SOF addressed these interactions of HIV PI/r and COBI with LDV and TDF differently, due to the general belief that participants on COBI regimens, such as elvitegravir (EVG)/COBI/TDF/FTC, would have other options for ARV switch, while participants on PI/r were less likely to have substituting options for ARVs. Studies with EVG/COBI/FTC/tenofovir alafenamide (TAF) and TDF/FTC/dolutegravir (DTG) are ongoing.

All ARVs will be allowed in the study as part of a highly active combination regimen at the recommended dose of the marketed product with the exception of **didanosine (ddl)** and **stavudine (d4T)** due to risk of hepatotoxicity, **zidovudine (ZDV)** due to risk of additive anemia with **RBV (RBV containing arms only)**, and **tipranavir boosted with ritonavir (TPV/r)** due to the predicted decrease in the concentrations of SOF when coadministered with TPV/r. The regimens containing TDF and COBI or ATV/r or DRV/r will be allowed in this study and participants will be monitored for renal toxicity. Plasma and intracellular samples will be obtained from all participants prior to initiating the study regimen, and throughout the course of treatment for assessments of potential drug interactions in participants exposed to LDV/SOF, TDF, and COBI, ATV/r or DRV/r should the need arise to investigate a potential interaction.

2.4 Spontaneous Clearance of HCV

Reported rates of spontaneous clearance of HCV among HIV-1 infected individuals are highly variable due to small sample sizes and significant variance across study populations. On average it is reported that 5-40% of HIV-1 infected individuals acutely infected with HCV will spontaneously clear the infection [Danta, 2008; Gambotti, 2005; Gilleece, 2005; Serpaggi, 2006]. Multiple baseline factors have been reported as predictive of clearance including female sex, host genetic factors including the IL28B favorable genotype, and early favorable HCV-RNA kinetics [Thomas, 2000; Soriano, 2008; Thomas 2009]. There are studies assessing viral kinetics in the early infection period and report ranges from 6%-48% of participants having detectable HCV RNA 12 weeks after first clinical evidence of infection and go on to spontaneously clear the infection [Gerlach, 2003; Mosley, 2008; Vogel, 2010]. Indeed on rare occasions participants have been reported to spontaneously clear the infection after 12-13 months or even longer [Larghi, 2002; Spada, 2004]. Many of these are very small, single center studies; however, the bulk of studies suggest that the majority of participants with acute HCV infection who will spontaneously clear will do so during the first 12 weeks (90-94%) [Corey, 2010]. Thus, it is a minority (6-10%) of participants who may receive treatment unnecessarily. These data must be balanced with the evidence that suggests a delay in initiation of therapy for acute HCV decreases the chance of achieving a sustained virologic response (SVR). A meta-analysis of early treatment in 417 HCV monoinfected participants reported that those participants who delayed therapy >12 weeks (63-67%) from diagnosis had lower SVR than those treated at or within 12 weeks of diagnosis

(83%) [Corey, 2010]. While this is in part due to inclusion of those **participants** who would spontaneously clear, it is also proposed to be due to the earlier preservation of multispecific HCV-specific T cell responses, which is thought critical to the ability to prevent HCV viral persistence [Kamal, 2004].

2.5 Overall Risk/Benefit Assessment

No clinical safety issues specifically related to SOF **or** LDV/SOF have been identified to date in HCV monoinfected or HIV-1/HCV coinfecting **participants**.

The expected benefits to **participants** being treated with SOF+RBV **or** LDV/SOF is a rapid and durable eradication of HCV virus without the side effects associated with the use of PEG and a shortened treatment period. Potential risks include unforeseen safety issues and unknown implications of virologic failure due to the emergence of resistant virus which is thought to be very low.

For the population of HIV-1/HCV coinfecting **participants**, the potential benefit of achieving SVR with 8 to 12 weeks of an IFN-free regimen outweighs the risks associated with the possible development of previously unidentified safety issues or the emergence of quasispecies resistant to SOF **or** LDV.

If high rates of SVR can be obtained with a shortened, IFN-free regimen, without frequent emergence of resistant HCV, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with acute HCV infection.

2.6 Adherence Measures

The efficacy of SOF+RBV **or** LDV/SOF for the treatment of acute HCV may be influenced by **participants'** adherence to the study medications. There is no perfect measure of adherence, but tools include pill counts, pharmacy refill records, self-report, directly observed therapy, measurement of drug concentrations, and electronic monitoring. This study will use a combination of these measures of adherence (see section 6.3.12).

3.0 STUDY DESIGN

A5327/SWIFT-C is an open-label, two-cohort clinical trial, in which between 44 and 50 acutely HCV (any genotype including mixed genotype infection) infected HIV-1 positive **participants** will be enrolled and administered oral SOF 400mg QD in combination with weight-based RBV (1000 or 1200 mg daily in two divided doses) **or the daily fixed dose combination of LDV/SOF (90mg/400mg)**.

The study will open the first cohort with treatment **with SOF+RBV** for 12 weeks **and a planned accrual of at least 17 participants**. Cohort 2 will enroll participants on LDV/SOF for an 8-week treatment course and a planned accrual of at least 27 **participants**. The total time to complete all study visits is approximately 36 weeks for

participants treated with **12** weeks of therapy and **32** weeks for **participants** treated with **8** weeks of therapy. **Both cohorts will be assessed for efficacy with SVR12 based on noninferiority criteria compared** to the study-defined historical SVR rate of 60%. The SVR of 60% was chosen based on a summary of nine acute HCV treatment studies in HIV-1 coinfecting **participants** identified in a recent report by the European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel [AIDS, 2011]. In this summary, 96 (60%) of 159 **participants** treated with PEG/IFN combined with RBV achieved SVR24 (ie, the conventional definition of SVR evaluated at 24 weeks after stopping treatment). This was felt to be the best representation of a historical control for this small, evidence-generating study. If a **participant** is discontinued from study treatment for nonvirologic reasons or is not evaluable for SVR12 while enrollment is ongoing to the same cohort, then an additional **participant** may be enrolled to that cohort to help ensure that an adequate number of **participants** complete study treatment up to a maximum enrollment of 50 **participants**. Each cohort will occur in two steps: on-treatment (Step 1) and followup (Step 2). The cohorts will enroll sequentially.

Potential **participants** who have met the enrollment definition for acute HCV will be consented and screened; however, they will not be eligible for study entry until an HCV RNA is confirmed to be detectable >12 weeks after first laboratory evidence of acute HCV (to confirm ongoing infection since a small percentage of **participants** will have spontaneously cleared virus). This confirmation may occur at screening if it is more than 12 weeks from first laboratory evidence of infection. If the screening visit occurs less than 12 weeks from the first laboratory evidence of infection, then the **participant** will require a pre-entry study visit to confirm detectable HCV RNA at least 12 weeks from the first laboratory evidence of infection have passed (see Figure I-1 in Appendix I). It is optimal for this pre-entry visit to occur as close as possible to 12 weeks from first laboratory evidence of acute infection to ensure timely treatment. Potential **participants** who enter screening but who have an undetectable HCV RNA (<LLOQ target not detected [TND]) at the pre-entry visit (when required) will have exhibited evidence of possible spontaneous clearance and will not meet the entry criteria.

4.0 SELECTION AND ENROLLMENT OF **PARTICIPANTS**

Cohort 1 completed accrual under A5327 Version 1.0. The eligibility criteria that are specific for Cohort 1 only have been removed from sections 4.1 and 4.2. The eligibility criteria in sections 4.1 through 4.4 apply to Cohort 2.

4.1 Step 1 Inclusion Criteria **for Cohort 2**

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a FDA-approved kit, which is required for all IND studies.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

- 4.1.2 A documented confirmation of acute HCV infection within 6 months prior to A5327 entry or HCV reinfection as described below:

Acute HCV infection will be defined as meeting one of the following criteria and exclusion of other causes of acute hepatitis:

- New (<24 weeks prior to initial A5327 **entry**) ALT elevation to $\geq 5X$ upper limit of normal (ULN) OR >250 U/L in **patients** with documented normal ALT in the preceding 12 months or $\geq 10X$ ULN OR >500 U/L in **patients** with abnormal or no measured ALT baseline in the preceding 12 months with detectable HCV RNA excluding those with any prior positive anti-HCV.

OR

- Detectable HCV RNA with prior negative anti-HCV Ab or undetectable HCV RNA within the preceding 6 months.

Acute HCV reinfection will be defined by documentation of clearance of prior infection (as evidenced by positive anti-HCV Ab) either spontaneously or after treatment with two negative HCV RNA a minimum of 6 months apart AND meeting one of the following criteria in addition to exclusion of other causes of acute hepatitis:

- New (<24 weeks prior to initial A5327 **entry**) ALT elevation to $\geq 5X$ ULN OR >250 U/L in **patients** with documented normal ALT in the preceding 12 months or $\geq 10X$ ULN OR >500 U/L in **patients** with abnormal or no measured ALT baseline in the preceding 12 months with detectable HCV RNA.

OR

- Positive HCV RNA with prior negative HCV RNA within the preceding 6 months.

- 4.1.3 HCV RNA confirmed to be detectable >12 weeks after first laboratory evidence of acute HCV and still within the <24 week from first laboratory evidence of acute HCV infection window. First laboratory evidence of infection is defined as date of first elevated liver enzymes or date of first serologic evidence of HCV seroconversion and/or viremia (whichever occurs first).

NOTE: If the screening visit occurs less than 12 weeks from the first laboratory evidence of infection, then the **participant** will require a pre-entry study visit to confirm detectable HCV RNA at least 12 weeks from the first laboratory evidence of infection have passed (see Figure I-1 in Appendix I). It is optimal for this pre-entry visit to occur as close as possible to 12 weeks from first laboratory evidence to ensure timely treatment. Potential **participants** who enter screening but who have an undetectable HCV RNA (<LLOQ TND) at the pre-entry visit (when required) will have exhibited evidence of possible spontaneous clearance and will not meet the entry criteria.

4.1.4 HCV genotype 1a, 1b, or 4 infection with source documentation from a CLIA-approved laboratory (or its equivalent).

NOTE: Those with mixed 1a/b genotype will be classified as 1a.

4.1.5 HIV-1 ARV therapy should fall into one of the following criteria:

- a) ARV untreated, for example due to (1) lack of indication per provider (CD4 T-cell count >500 cells/mm³) or (2) decision by provider and **participant** to defer ARV therapy during the study drug dosing period (8 or 12 weeks), or (3) elite controller (CD4+ >200 cells/mm³).

OR

- b) On a stable, protocol-approved ARV regimen (**the following ARVs are not allowed: ddl, d4T, and TPV/r**) for >8 weeks prior to screening with a CD4 T-cell count >200 cells/mm³ and a documented plasma HIV-1 RNA level <50 copies/mL **or <LLOQ of local assay if LLOQ is >50 copies/mL** by any laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent ≥ 8 weeks preceding the A5327 screening visit. HIV-1 RNA levels should be within 1 year of the screening visit. Screening HIV-1 RNA must be <50 copies/mL as measured by any local laboratory using an FDA-approved assay.

4.1.6 Body mass index (BMI) ≥18 kg/m²

4.1.7 Candidates must have the following laboratory parameters within 10-42 days prior to study entry:

- a) Hemoglobin ≥9 g/dL for male **and** female **participants**
- b) International normalized ratio (INR) ≤1.5 x ULN unless **participant** has known hemophilia or is stable on an anticoagulant regimen affecting INR
- c) Albumin ≥3 g/dL
- d) Creatinine clearance (CrCl) ≥60 mL/min, as calculated by the Cockcroft-Gault equation (refer to section 6.3.5 for calculator utility link)

4.1.8 Screening electrocardiogram (ECG) without clinically significant abnormalities as determined by the investigator.

4.1.9 Willing and able to provide written informed consent.

4.1.10 Men and women age ≥ 18 years.

4.1.11 Female **participants** of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, ie, who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy) must have a negative serum **or urine** pregnancy test within 48 hours prior to study entry **by any laboratory or clinic that has a CLIA certificate or its equivalent, or is using a point-of-care (POC)/CLIA-waived test. The serum, urine or POC pregnancy test must have a sensitivity of at least 25 mIU/mL.**

4.1.12 All **participants** must agree not to participate in a conception process (eg, active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization).

NOTE: Female candidates who are pregnant or breastfeeding are not eligible. A male candidate who has a pregnant female partner is not eligible for the study.

4.1.13 When participating in sexual activity that could lead to pregnancy, all **participants** must agree to use at least two reliable forms of contraceptive simultaneously while receiving protocol-specified medications, and for 6 months after stopping the medications. Such methods include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptive

NOTE: Providers and **participants** should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Study **participants** who are sexually active with HIV-1 negative or unknown HIV-1 serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study. Study **participants** should discuss contraceptive choices and HIV risk reduction methods with their health care provider.

4.1.14 **Participants** who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy and/or bilateral oophorectomy or salpingectomy or men who have documented azoospermia or undergone vasectomy) are eligible without requiring the use of

contraceptives. Acceptable documentation of sterilization and menopause is specified below.

Written or oral documentation communicated by clinician or clinician's staff of one of the following:

- Physician report/letter
- Operative report or other source documentation in the patient record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Follicle stimulating hormone-release factor (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

4.1.15 Intention to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

4.2 Step 1 Exclusion Criteria for Cohort 2

4.2.1 Received investigational drug or device within 60 days prior to study entry.

4.2.2 **Any preceding attempt at HCV treatment during this acute HCV infection episode, ie, 24 weeks prior to entry.**

4.2.3 Chronic liver disease of a non-HCV etiology (eg, hemochromatosis, Wilson's disease, α 1 antitrypsin deficiency, **primary sclerosing** cholangitis).

4.2.4 Presence of active or acute AIDS-defining opportunistic infections within 30 days prior to study entry.

NOTE: A list of AIDS-defining opportunistic infections as defined by the CDC, can be found in Appendix B of the following document:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>

4.2.5 Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotics, antivirals, or antifungals within 30 days prior to study entry.

4.2.6 Infection with hepatitis B virus (HBV) defined as HBsAg positive.

4.2.7 Evidence of acute hepatitis A infection defined as HAV IGM positive.

4.2.8 Chronic use of systemically administered immunosuppressive agents (eg, prednisone equivalent >10 mg/day).

4.2.9 History of solid organ transplantation.

4.2.10 Current or prior history of clinical hepatic decompensation (eg, ascites, encephalopathy or variceal hemorrhage).

- 4.2.11 History of a gastrointestinal disorder (or post operative condition) that could interfere with the absorption of the study drug.
- 4.2.12 History of significant or symptomatic pulmonary disease, cardiac disease, or porphyria.
- 4.2.13 History of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.
- 4.2.14 History of clinically significant illness or any other major medical disorder that may interfere with **participant** treatment, assessment, or compliance with study requirements, which may include active drug or alcohol use or dependence.
- 4.2.15 Use of any prohibited concomitant medications within 30 days prior to study entry.
- 4.2.16 Known hypersensitivity to SOF **or** **LDV**, the metabolites, or formulation excipients or any other contraindication to the use of SOF or **LDV**.
- 4.2.17 Currently receiving **TPV/r**, **ddl**, **d4T** **or** **amiodarone**.
- 4.2.18 Acute HIV infection defined as the phase immediately following infection during which anti-HIV antibodies are undetectable.

NOTE: **Participants** with early infection, defined as within the first 6 months of infection and with a positive HIV antibody, should be discussed with the A5327 protocol core team. These **participants** may be considered for inclusion in the study on a case by case basis with the specific documented approval of the protocol chairs.

4.2.19 Pregnancy or Breastfeeding

4.3 Step 2 Inclusion Criteria for Cohort 2

- 4.3.1 Completion or premature discontinuation (including HCV VF) of Step 1 study treatment regimen.

NOTE: See section 8.1 for premature treatment discontinuation.

4.4 Step 2 Exclusion Criteria for Cohort 2

- 4.4.1 Premature study discontinuation.

NOTE: See section 8.2 for premature study discontinuation.

4.5 Study Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by their local institutional review board (IRB) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF WILL NOT be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the **participant**. The **participant** will be asked to read and sign the approved protocol consent form.

For **participants** from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

For **participants** from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.6 Coenrollment Guidelines

Sites are encouraged to coenroll **participants** in A5128, "Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses." Coenrollment in A5128 does not require permission from the A5327 protocol chairs.

For specific questions and approval for coenrollment in other studies, sites should first check the A5327 protocol specific web page (PSWP) or contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as sofosbuvir (SOF) in combination with weight based ribavirin (RBV) **or the daily fixed dose combination (FDC) of ledipasvir/sofosbuvir (LDV/SOF)**.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Between 44 and 50 acutely HCV infected, HIV-1 positive **participants** will be enrolled in one of two successive cohorts (these cohorts will be enrolled sequentially).

Cohort 1 (12-week treatment duration)

At least 17 **participants** will receive:

- SOF 400 mg, one tablet PO every morning with food.
- Weight-based RBV PO BID, every morning and every evening, with food (see Table 4 for actual dose)

Table 4 Weight-based RBV Dose

Weight (kg)	Morning Dose	Evening Dose
< 75 kg	600 mg (3 tablets)	400 mg (2 tablets)
≥ 75 kg	600 mg (3 tablets)	600 mg (3 tablets)

Total daily dose has been divided into two doses. The dose of RBV will be based on **participant's** weight at entry. Changes in weight after entry do not require a change in dose. Doses will only be changed for toxicity management.

Cohort 2 (8-week treatment duration)

At least 27 **participants** will receive:

- **LDV/SOF (90/400 mg), one tablet PO every morning**

5.1.2 Administration

5.1.2.1 SOF+RBV regimen

SOF should be taken with RBV. **Participants** should be instructed to take all doses of SOF and RBV with food. Study drug should be taken at the same times and maintain the same time intervals every day.

If a **participant** forgets to take the SOF at the correct time, it may be taken later in the day; however, no more than one 400 mg dose of SOF should be taken on any calendar day. The **participant** should resume the standing dosing schedule on the next day. Study medications should not be cut or split. If **participants** miss a dose of RBV, then they should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then the missed dose should be skipped, and the normal dosing schedule should be resumed. **Participants** should not double the next dose of either study drug in order to "make up" what had been missed.

5.1.2.2 LDV/SOF regimen

FDC LDV/SOF tablets should be taken once daily and without regard to food.

FDC LDV/SOF should be taken on a regular dosing schedule. If a participant does not take a dose at the regular time, it should be taken as soon as they remember on the same day. The participant should resume the usual dosing schedule the next day.

Participants should not take more than 1 tablet of FDC LDV/SOF in a day.

5.1.3 Duration

Study treatment may continue for a period of 8 to 12 weeks (as assigned at study entry). Study followup will be 24 weeks post treatment regardless of cohort. The study will be conducted for up to a total of 36 weeks.

5.2 Study Product Formulation

5.2.1 Formulation

SOF tablets, 400 mg, are yellow, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "7977" on the other side. In addition to the active ingredient, SOF tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinylalcohol, titanium dioxide, macrogol, talc, and yellow iron oxide.

RBV 200 mg tablets are light pink to pink, round, bicovex, beveled, film-coated tablets debossed with the logo of "ZC19" on one side and plain on the other side.

FDC LDV/SOF tablets are orange, diamond-shaped, film-coated tablets containing 400 mg of SOF and 90 mg of LDV. The tablets are debossed with "GSI" on one side and "7985" on the other side. The LDV/SOF FDC tablet contains the following inactive ingredients: lactose monohydrate,

copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, and FD&C yellow # 6 /sunset yellow FCF aluminum lake.

5.2.2 Storage

SOF bottles should be stored at a controlled room. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

RBV tablets should be stored at 20°C - 25°C (68°F - 77°F).

FDC LDV/SOF tablets should be stored at room temperature below 30°C (86°F). FDC LDV/SOF may be dispensed only in the original container.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Gilead Sciences, Inc. will manufacture and supply SOF **and FDC LDV/SOF** for this study. Zydus will manufacture RBV. Study products will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section *Study Product Management Responsibilities*.

ART will not be provided through the study.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products in US CRSs must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section *Study Product Management Responsibilities*.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the **ACTG Precautionary and Prohibited Medications Database** located at: http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

See inclusion criteria (section 4.1) for specifications about ART. Changes to ART must be discussed with the A5327 protocol core team during the study drug dosing period.

5.4.2 Prohibited Medications

For a list of prohibited medications, please refer to the A5327 PSWP.

5.4.3 Colony Stimulating Agents

Under no circumstances are potential **participants** to be treated with colony stimulating agents (CSA) during screening to elevate hematology laboratory parameters to facilitate entry into the study. CSAs, such as erythropoiesis stimulating agents or granulocyte colony-stimulating factor, will not be provided by the study.

6.1 Schedule of Events

[illegible]

Evaluations	Screening	Pre-Entry (see section 6.2.1)	Entry (day 0)	On-Treatment Study Visits					HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Disc
	Within 10-42 days prior to entry			Wk 1	Wk 2	Wk 4	Wk 8	Wk 12			
				See section 6.2.3 for visit windows							
Plasma HCV RNA (screening and pre-entry performed at local lab, see section 6.3.6)	X	X									
Plasma HCV RNA (real-time)			X	X	X	X	X	X	X ²		X
Plasma HCV Genotype Test (screening performed at local lab unless unavailable, see section 6.3.6)	X										
Plasma HIV-1 RNA (real-time, see section 6.3.6)	X		X			X		X		X ³	X
Plasma HIV-1 RNA Resistance Testing (real-time genotyping, see section 7.4)										X ⁴	
Stored Serum and Plasma for HIV-1/HCV Studies (see section 6.3.6)			X			X	X	X	X	X	X
CD4+/CD8+	X		X					X			X
Stored Plasma and PBMC (see section 6.3.7)			X	X		X		X	X		X
Additional Stored Samples (see section 6.3.8)			X					X			

Evaluations	Screening	Pre-Entry (see section 6.2.1)	Entry (day 0)	On-Treatment Study Visits					HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Disc
	Within 10-42 days prior to entry			Wk 1	Wk 2	Wk 4	Wk 8	Wk 12			
				See section 6.2.3 for visit windows							
PK Sampling			X	X	X	X	X	X	X	X	X
IL28B Genotype (see section 6.3.10)	X		If needed								
ITPA Genotype (see section 6.3.10)			X								
Pregnancy Prevention Counseling			X			X		X			X
Adherence Assessment (see section 6.3.12)				X	X	X	X	X			X
Study Drug Dispensing			X			X	X				

¹ Although a fasting lipid panel is not required at screening, sites should make every effort to get **participants** to come to the clinic in a fasting state for the lipid panel at the designated study visits.

² An increase in **plasma** HCV RNA at any time point meeting HCV virologic-based treatment stopping criteria must be confirmed with repeat testing within 2 weeks. For more information please see section 7.3.

³ HIV-1 viral breakthrough, as defined in section 7.4, should be confirmed with repeat testing as soon as possible, not to exceed 4 weeks.

⁴ This specimen should be drawn at the time of HIV-1 treatment failure confirmation and shipped to the designated VSL. Please see section 7.4.

⁵ **The weight recorded at entry will be used as the weight for PK analysis and reported in the PK CRF for the weeks 1, 2, 4, and 8 visits and the HCV and HIV-1 VF Confirmation visits.**

6.1.2 Step 1 –Study Visits for 8-week Treatment (for Cohort 2)

Evaluations	Screening	Pre-Entry (see section 6.2.1)	Entry (day 0)	On-Treatment Study Visits				HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Disc
	Within 10-42 days prior to entry			Wk 1	Wk 2	Wk 4	Wk 8			
				See section 6.2.3 for visit windows						
HIV-1 Documentation	X									
Medical History	X									
Medication History	X		X							
Clinical Assessments	X		X	X	X	X	X			X
Weight	X		X ¹				X			X
12-lead ECG	X									
Hematology and Chemistries	X	If needed	X	X	X	X	X			X
Calculated CrCl	X	X	X	X	X	X	X			X
Lipid Panel (fasting) ²	X (see section 6.2.1)		If needed			X	X			X
Coagulation Markers	X	If needed	X				X			X
Urinalysis			X		X ³	X ³	X ³			X ³
Pregnancy Test (see section 6.3.5)	X	If needed	X			X	X			X
Serologies (see section 6.3.5)	X									
Plasma HCV RNA (screening and pre-entry performed at local lab, see section 6.3.6)	X	X								
Plasma HCV RNA (real-time)			X	X	X	X	X	X ⁴		X

Evaluations	Screening	Pre-Entry (see section 6.2.1)	Entry (day 0)	On-Treatment Study Visits				HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Disc
	Within 10-42 days prior to entry			Wk 1	Wk 2	Wk 4	Wk 8			
				See section 6.2.3 for visit windows						
Plasma HCV Genotype Test (screening performed at local lab unless unavailable, see section 6.3.6)	X									
Plasma HIV-1 RNA (real-time, see section 6.3.6)	X		X			X	X		X ⁵	X
Plasma HIV-1 Resistance Testing (real-time genotyping, see section 7.4)									X ⁶	
Stored Serum and Plasma for HIV- 1/HCV Studies (see section 6.3.6)			X			X	X	X	X	X
CD4+/CD8+	X		X							X
Stored Plasma and PBMC (see section 6.3.7)			X	X		X	X	X		X
Additional Stored Samples (see section 6.3.8)			X				X			
PK Sampling			X	X	X	X	X	X	X	X
IL28B Genotype (see section 6.3.10)	X		If needed							
ITPA Genotype (see section 6.3.10)			X							
Pregnancy Prevention Counseling			X			X	X			X
Adherence Assessment (see section 6.3.12)				X	X	X	X			X

Evaluations	Screening	Pre-Entry (see section 6.2.1)	Entry (day 0)	On-Treatment Study Visits				HCV VF Confirmation	HIV-1 VF Confirmation	Prem. Tx/Study Disc
	Within 10-42 days prior to entry			Wk 1	Wk 2	Wk 4	Wk 8			
				See section 6.2.3 for visit windows						
Study Drug Dispensing			X ⁷							

¹ The weight recorded at entry will be used as the weight for PK analysis and reported in the PK CRF for the weeks 1, 2, and 4 visits and the HCV and HIV-1 VF Confirmation visits.

² Although a fasting lipid panel is not required at screening, sites should make every effort to get **participants** to come to the clinic in a fasting state for the lipid panel at the designated study visits.

³ **Urinalysis will be required at on treatment weeks 2, 4, and 8 for all participants on TDF as part of their HIV regimen.**

⁴ An increase in **plasma** HCV RNA at any time point meeting HCV virologic-based treatment stopping criteria must be confirmed with repeat testing within 2 weeks. For more information please see section 7.3.

⁵ HIV-1 viral breakthrough, as defined in section 7.4, should be confirmed with repeat testing as soon as possible, not to exceed 4 weeks.

⁶ This specimen should be drawn at the time of HIV-1 treatment failure confirmation and shipped to the designated VSL. Please see section 7.4.

⁷ **Dispense two bottles of study drug and ensure participant understands dosing instruction.**

6.1.3 Step 2 –Post treatment Study Visits Following Last Dose of Study Treatment (Cohorts 1 and 2)

Evaluations	EOT	Post Treatment (PTx) Period					Prem Study Disc
	Date of last dose	Wk 2 PTx	Wk 4 PTx	Wk 8 PTx	Wk 12 PTx	Wk 24 PTx	
		See section 6.2.3 for visit windows					
Clinical Assessments		X	X	X	X	X	X
Weight					X	X	X
Hematology and Chemistries		X	X	X ³	X ³		X ⁴
Calculated CrCl		X⁵	X⁵	X⁵	X⁵		X⁵
Lipid Panel (fasting) ¹					X		X
Urinalysis		X⁶	X⁶		X⁶		X⁶
Pregnancy Test (see section 6.3.5)			X	X	X	X	X
Serum HCV RNA ² (real-time)		X	X	X	X	X	X
Plasma HIV-1 RNA (real-time, see section 6.3.6)							X
Stored Serum and Plasma for HIV-1/HCV Studies (see section 6.3.6)		X	X	X	X	X	X
CD4+/CD8+					X	X	X
Stored Plasma and PBMC (see section 6.3.7)		X	X		X	X	X
PK Sampling		X	X	X	X		X
Pregnancy Prevention Counseling		X	X	X	X	X	X

¹ Sites should make every effort to get **participants** to come to the clinic in a fasting state for the lipid panel at the designated study visits.

² A detectable HCV RNA after the end of treatment is virologic evidence of relapse which will require confirmation and should be performed in real time at the designated VSL as soon as possible but no later than 2 weeks.

³ **For Cohort 2 only: Creatinine required at post treatment weeks 8 and 12 for all participants on TDF as part of their HIV regimen.**

⁴ **Cohort 1: Only** required if study discontinuation occurs before week 4 PTx visit. **Cohort 2: Required at study discontinuation.**

⁵ **For Cohort 2 only: Calculated CrCl required at post treatment weeks 2, 4, 8, and 12 for all participants on TDF as part of their HIV regimen.**

⁶ **For Cohort 2 only: Urinalysis required at post treatment weeks 2, 4, and 12 for all participants on TDF as part of their HIV regimen.**

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening

Screening evaluations must occur prior to the **participant** starting any study medications, treatments, or interventions and, if possible, should be done in a fasting state (defined in section 6.3.5). Although fasting is not required for the screening visit, the site should make every effort to get the potential **participant** to come back to the clinic within 7 days of the originally scheduled screening visit for a fasting lipid panel.

Screening evaluations to determine eligibility must be completed within 10-42 days prior to entry unless otherwise specified.

In addition to data being collected on **participants** who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

Pre-Entry

Pre-entry evaluations must occur at least 24 hours after screening evaluations have been completed, unless otherwise specified.

The pre-entry visit will be required for those **participants** whose screening visit is less than 12 weeks from the first laboratory evidence of acute infection.

NOTE: If the screening period is extended past 6 weeks (ie, more than 42 days) to meet the criterion for detectable HCV RNA >12 weeks from first laboratory evidence of acute infection, safety lab tests (hematology, chemistry, coagulation markers, pregnancy test) will need to be repeated at pre-entry with results available at the site so enrollment can occur.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after pre-entry (if required) evaluations have been completed and/or at least 10 days after screening, unless otherwise specified.

Participant must begin treatment within 24 hours after registration.

NOTE: Entry evaluations must be performed prior to dosing. **Participant** must be fasting (no food or drink, except water for taking prescription medications, for at least 8 hours).

6.2.3 Post-Entry Evaluations

All post-entry evaluations occur in reference to the date of study entry.

On-Treatment Evaluations

Weeks 1 and 2 have a window of ± 3 days. Weeks 4, 8, and 12 have a window of -7 days and $+14$ days.

Post-Treatment Evaluations

After the last dose of study drugs, the PTx study visits have the following windows:

- Week 2 PTx: -5 days to $+7$ days
- Weeks 4 and 8 PTx: -5 days to $+21$ days
- Week 12 PTx: -5 days and $+28$ days
- Week 24 PTx: -7 days and $+28$ days

Study Completion Evaluations

The week 24 PTx visit will be completed as the **participant's** final study visit.

6.2.4 Discontinuation Evaluations

Evaluations for Registered **Participants** Who Do Not Start Study Treatment

Participants who do not start study treatment will be taken off study with no further evaluations required.

All CRFs must be completed and keyed for the period up to and including entry.

HCV Virologic Failure

Participants who permanently discontinue study treatment for HCV virologic failure (see details in section 7.3) will be followed on study/off treatment through the week 24 PTx visit.

Premature Treatment Discontinuation Evaluations

The protocol core team must be informed, as soon as possible, when a **participant** comes off study treatment due to an AE. **Participants** who permanently discontinue study treatment for toxicity or any other reason, and who have not met the HCV virologic failure criteria defined in section 7.3 will also follow the schedule in section 6.1.2. If applicable, additional or more frequent post-treatment toxicity followup may be determined by the site investigator.

Participants who prematurely discontinue study treatment (ie, prior to completion of the last dose of SOF+RBV or LDV/SOF per the assigned dosing period) will complete the treatment discontinuation evaluations. **Participants** discontinuing study treatment prematurely will remain on study and complete PTx visits at 2, 4, 8, 12, and 24 weeks from the date on which the **participant** took the last dose of study treatment.

NOTE: If SOF is discontinued, **participants** should discontinue RBV. Under no condition should the **participant** remain on RBV monotherapy.

For **participants** who discontinue the study treatment due to AEs or death, please document and record the following information on the CRFs:

- All concomitant medications
- Basis for determining that the AE was due to the study drug
- **Participant** history of same AE or AEs similar to the one that resulted in discontinuation and when they occurred if known
- Onset date of AE that led to discontinuation and actual date of discontinuation

Pregnancy

Pregnancy will result in immediate and permanent discontinuation of the study medications. Please see section 7.2 for detailed information regarding **participant** management.

Premature Study Discontinuation Evaluations

Participants who prematurely discontinue from the study will have the study discontinuation evaluations performed prior to being taken off the study.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document: <http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf>

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the **participant** or may require intervention to prevent one of the events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

In addition to reporting all diagnoses within the past 30 days, the following diagnoses should be reported for all ACTG studies regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B

In addition, the medical history must include all clinical events and diagnoses identified by Appendix 100 targeted for A5327. For current criteria, refer to the A5327 PSWP.

Any allergies to any medications and their formulations must also be documented.

6.3.3 Medication History

A medication history must be present, including start and stop dates. Table 3 below lists the medications that must be included in the history.

Table 3: Medication History

Medication Category	Complete History or Timeframe
HIV treatment	Within 42 days prior to entry
HCV treatment	Complete history
Prescription drugs for treatment of opportunistic infections	Within 42 days prior to entry
Prescription drugs for prophylaxis of opportunistic infections	Within 42 days prior to entry
Other prescription drugs	Within 42 days prior to entry
Proton-pump inhibitors (Cohort 2 only)	Within 42 days prior to entry
Non-prescription drugs	Within 42 days prior to entry
Complementary and alternative therapies	Within 42 days prior to entry

6.3.4 Clinical Assessments

Complete Physical Exam

A complete physical examination must be performed at screening and is to include at a minimum an examination of the head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

Targeted Physical Exam

A targeted physical examination must be performed at entry and all subsequent visits. It should include vital signs (temperature, pulse, and respiratory rate, and resting blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the **participant** has experienced since the last visit.

NOTE: Blood pressure will be measured following the current ACTG Standardization of Blood Pressure Measurement SOP.

Height

Record height at screening.

Weight

Record weight as indicated in section 6.1.

NOTE: Weight should be done with inner clothing and without shoes.

BMI

BMI should be calculated using standard formula.

12-Lead ECG

An electrocardiogram (ECG) will be performed at screening.

NOTE: **Participant** should rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for gross abnormalities.

Signs and Symptoms

At entry, all signs and symptoms, regardless of grade, that occurred within 42 days prior to study entry must be recorded. Post-entry, only signs and symptoms Grade ≥ 2 must be recorded. Record all signs and symptoms that led to a change in treatment (excluding indications for RBV dose reduction), regardless of grade.

Diagnoses

Refer to section 6.3.2 for the diagnosis reporting requirements in the medical history at screening.

At entry and thereafter, only the diagnoses identified as targeted for A5327 should be reported. Refer to the A5327 PSWP.

Concomitant Medications

Record new or discontinued concomitant prescription and nonprescription medications taken since the last on treatment study visit and at the weeks 2, 4, 8, 12, and 24 PTx visits.

Start and stop dates of all prescription and all nonprescription medications will be recorded on the CRF.

Study Treatment Modifications

Record all study drug modifications, including initial doses, **participant**-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions at each visit. Record any permanent discontinuation of treatment.

6.3.5 Laboratory Evaluations

At screening, pre-entry, and entry all laboratory values must be recorded. For post-entry assessments, record all Grade ≥ 2 laboratory values. All laboratory toxicities that led to a change in treatment (excluding indications for RBV dose reduction), regardless of grade, must be recorded.

Fasting Instructions

Fasting is defined as nothing to eat or drink except prescription medications and water for at least 8 hours. If **participants** are in a nonfasting state, they can have a fasting blood draw at the next scheduled study visit, as indicated in section 6.1. If nonfasting at the screening visit, the **participant** should return within 7 days for fasting blood draw.

Hematology

Hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count, and MCV.

Chemistries

Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, alkaline phosphatase, creatinine, total bilirubin, direct bilirubin, glucose, lipase, potassium, thyroid-stimulating hormone, and sodium.

At entry only, gamma-glutamyl transferase.

Calculated CrCl

Estimated each time that a creatinine level is determined **during the on-treatment period. At the post treatment period, estimate only in Cohort 2**

participants who are taking TDF as part of their HIV regimen (refer to section 7.1.2).

To estimate calculated CrCl, use the following method of Cockcroft and Gault:

- For men: $[(140 - \text{age in years}) \times (\text{body weight in kg})] \div (\text{serum creatinine in mg/dL} \times 72)$.
- For women: use the same calculation as for men, then multiply the result by 0.85.

A calculator is available at the DMC Web site:

<https://www.fstrf.org/ACTG/ccc.html>.

Lipid Panel (fasting)

Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), total cholesterol (TC), and apolipoproteins B, E, and CIII (**performed at the designated testing laboratory; see A5327 laboratory processing chart [LPC] for directions**).

Fasting lipid panel should only be performed at entry if not done at screening.

Coagulation Markers

INR, prothrombin time (PT), activated partial thromboplastin time (APTT).

Urinalysis

Appearance, blood, color, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Pregnancy Test

For women with reproductive potential: a serum β -HCG, **urine or POC/CLIA-waived test** documenting a negative result will be required within 48 hours prior to study entry. **The test** should have a sensitivity of at least 25 mIU/mL.

Once a **participant** has enrolled with a negative documented serum pregnancy test and begins using 2 forms of contraception to prevent pregnancy, further testing per section 6.1 (during study drug dosing and in post treatment followup) can be urine testing. Urine test must have a sensitivity of at least 50 mIU/mL; if positive, must have immediate confirmation with serum β -HCG.

All females of reproductive potential will have a pregnancy test, as indicated in sections 6.1.1 and 6.1.2. In the event of a positive urine pregnancy result, **participants** will be instructed to stop study drugs immediately and return to the clinic as soon as possible for a serum pregnancy test. See section 7.2 for detailed information regarding study management.

Serologies

HCV Ab, HAV IgM, and HbsAg will be done during screening with results available prior to study entry.

If a historical HIV Ab test result (ie, used for HIV-1 infection documentation to meet inclusion criterion 4.1.1) is not available, an HIV Ab test will also be done at screening with the result available prior to study entry.

6.3.6 Virologic Studies

Plasma HCV RNA (screening and pre-entry)

The screening and pre-entry HCV RNA result must be obtained by any FDA-approved test for quantifying HCV RNA at any local laboratory that has a CLIA certification or its equivalent. Screening HCV RNA must be obtained within 10-42 days prior to study entry.

The pre-entry HCV RNA will be obtained to confirm ongoing infection prior to study entry.

Plasma HCV RNA (on-study evaluations)

At the entry and post-entry visits, HCV RNA quantification will be performed at the designated testing laboratory as follows:

Plasma HCV RNA real-time testing will be collected, processed, and shipped to the designated testing laboratory (see A5327 LPC for directions). These results will be reported within 2 weeks after specimen receipt.

HCV Genotype

At screening, the HCV genotype result will be obtained locally (**real-time**) from any laboratory that has a CLIA certification or its equivalent. ONLY IF IT IS NOT AVAILABLE LOCALLY should it be done (**real-time**) at the designated testing laboratory (see A5327 LPC).

Plasma HIV-1 RNA

A documented plasma HIV-1 RNA level must be noted within 10-42 days prior to study entry from any laboratory that has a CLIA certification or its equivalent. On-study HIV-1 RNA should be performed at **the ACTG central laboratory**. See the LPC for processing, shipping, and storage information.

Participants on ART who later experience HIV-1 viral breakthrough while on HIV therapy should be managed as per section 7.4.

Stored Serum and Plasma for HIV-1/HCV Studies

Serum and plasma samples will be collected and stored for potential HCV and HIV sequencing and other virology studies. For processing and shipping instructions, refer to the A5327 LPC.

6.3.7 Immunologic Studies

CD4+/CD8+

Screening CD4+/CD8+ testing may be done by any laboratory that possesses a CLIA certification or its equivalent.

During the study, all laboratories must possess a CLIA certification or its equivalent and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

Stored Plasma and PBMC

Stored plasma and PBMC will be collected, processed, and shipped to the designated immunology laboratory for testing of host ISGs proteins, and T cell immune responses will be evaluated (see A5327 LPC). Plasma will be used to assess protein levels of selected ISGs and PBMCs will be used to assess for CD4+/CD8+ T-cell responses and intracellular RNA expression of selected ISGs.

DNA for host polymorphisms: DNA will be extracted from PBMC and stored for single nucleotide polymorphism (SNP) testing for key loci.

6.3.8 Additional Stored Samples

Stored plasma will be collected at the indicated visit (see section 6.1) for future testing and shipped according to the A5327 LPC. This additional blood will be collected from **participants** who consent to this collection; these samples will be used for future ACTG-approved research.

6.3.9 PK Sampling

For dried blood spots (DBS) **and** plasma for PK, please refer to section 10.2.

6.3.10 IL-28B and ITPA Genotype

Whole blood will be obtained and shipped batch to the designated immunology laboratory for testing of specific genetic variants; these samples will be analyzed for IL28B and ITPA genotype. IL28B and ITPA genotype will be determined by polymerase chain reaction (PCR) amplification by the designated immunology laboratory (see A5327 LPC). For processing and shipping instructions, refer to the A5327 LPC.

IL28B genotype will be completed on all **participants** who consent to this collection regardless of whether the **participant** enrolls into the study. At entry, only collect the sample for IL28B genotype if it was not obtained during screening.

The ITPA genotype will be performed only on **participants** who consent to this collection and are subsequently enrolled into the study.

6.3.11 Pregnancy Prevention Counseling

Counseling on pregnancy prevention will be conducted as per site's standard of care.

6.3.12 Adherence Assessment

This study will use a combination of three measures of adherence (1) the Adult ACTG 4-day recall, (2) pill count, and (3) measurement of RBV concentrations.

Adherence questionnaire will be used to determine **participant** adherence to antiretroviral medications and study medications.

Study drug and dosing diary will be reconciled at all on-treatment visits by the site staff/investigator in order to monitor the **participant's** adherence with the study drug regimen.

6.3.13 Study Drug Dispensing

Participants must be instructed to bring back all bottles of study drugs in the original container at the post-entry study visits, as indicated in section 6.1.

For Cohort 2 only: At the entry visit two bottles of study drug will be dispensed to participants (ie, 8 weeks supply of study drug). The site staff/investigator must confirm that participants understand the dosing instructions to ensure 8 weeks of continuous dosing.

7.0 CLINICAL MANAGEMENT ISSUES

Criteria for **participant** management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to study drugs (ie, SOF and RBV **or** LDV/SOF).

The grading system for drug toxicities is located in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

NOTE: The team must be notified via e-mail within 72 hours regarding toxicities that result in a change in study regimen (actg.corea5327@fstf.org).

7.1 Toxicity

It is possible that some **participants** will experience transient or prolonged AEs during the trial. Some **participants** may need to adjust RBV dosing. To minimize the effects of

these dosing modifications on the eventual evaluation of the safety, tolerability, and activity of study treatment, the principles in the following sections will be used to determine the appropriate dose adjustment.

Grades 1 and 2 AEs associated with SOF or RBV **or LDV/SOF** require no change in study treatment but close followup; with the exception that modifications of RBV dosing for Grades 1 and 2 anemia are provided in section 7.1.1.

7.1.1 Management of Side Effects of RBV

The most common AE of RBV therapy is anemia due to hemolysis. Anemia typically occurs within 1 to 2 weeks of initiating RBV therapy and usually resolves within 4 to 8 weeks of drug discontinuation or dose reduction. Indirect bilirubin elevation is commonly seen in those **participants** with anemia secondary to RBV-induced hemolysis.

Another major side effect of RBV is its teratogenicity; it is therefore strongly recommended that pregnant women or breastfeeding women and men with pregnant sexual partners not receive RBV. Women who become pregnant on study and men on study whose partners become pregnant must discontinue study treatment and complete the discontinuation evaluations as indicated in section 7.2.

RBV dosing in this study will be based on weight at study entry (see section 5.0). Dose reduction of RBV is the recommended management for ribavirin associated anemia and should be performed according to the product label. Information is summarized in Table 7-1. It is recommended that sites contact the protocol core team with questions regarding difficult anemia management and/or if it is felt ribavirin discontinuation is required. **Participants** may continue to take SOF if RBV is temporarily or permanently discontinued.

Table 7-1. Suggested RBV Dose Reduction in the Event of Anemia

Laboratory Values	Reduce RBV Dose to 600 mg/day if:	HOLD RBV if:
Hemoglobin in participants with no cardiac disease	<10 g/dL	<8.0 g/dL
Hemoglobin in participants with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week period treatment	<10 g/dL despite 4 weeks at reduced dose
Symptomatic drop in hemoglobin to be managed at the discretion of the site investigator and can be discussed with the protocol chairs.		

Reintroduction of RBV

If RBV is temporarily stopped due to anemia, the hemoglobin must be rechecked within 2 weeks and at 2-week intervals until stable. Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may

be made to restart RBV at 600 mg daily in two divided doses and further increase the dose to 800 mg daily in two divided doses. However, it is not recommended that RBV be increased to the original assigned dose. Please refer to the table below for dosing intervals.

Daily Dose	Morning Dose	Evening Dose
600 mg	400 mg (2 tablets)	200 mg (1 tablet)
800 mg	400 mg (2 tablets)	400 mg (2 tablets)

NOTE 1: The half-life of RBV in **patients** with normal renal function is 290 hours.

NOTE 2: The ranges of hemoglobin values used as criteria for triggering dose reduction of RBV do not correspond to those used to grade toxicities in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009). Therefore, sites are expected to use A5327-specific criteria.

7.1.2 Management of Side Effects of SOF or LDV/SOF

To date, there has been no safety signal identified that is attributable to SOF or LDV/SOF when administered as part of a combination regimen. However if a SAE occurs, administration of SOF or LDV/SOF may be discontinued due to a clinical or laboratory event. **TFV levels, when given with LDV/SOF, are anticipated to be similar to those achieved with boosted protease inhibitor (PI)-based regimens. For participants also on a RTV boosted HIV PI or a COBI-containing regimen there is potential for higher exposures. Thus, renal monitoring will be implemented during on-treatment and post treatment visits of the study for those participants taking TDF. Renal monitoring in Cohort 2 will include serum glucose, potassium, creatinine, and calculated creatinine clearance at screening, entry, every on-treatment visit, and at the post treatment weeks 2 and 4 visits and then followed by serum creatinine and calculated creatinine clearance at the post treatment weeks 8 and 12 visits. Urinalysis will be completed at entry, on-treatment weeks 2, 4, and 8, and post treatment weeks 2, 4, and 12.**

Protocol defined changes in renal function will include creatinine clearance <50 mL/min (confirmed within 5 days), increase in creatinine >0.4 mg/dL (confirmed within 2 weeks), and new 2+ proteinuria (confirmed within 2 weeks). If any of these occur the site investigator should contact the protocol team immediately to discuss further management. No changes in LDV/SOF or the HIV regimen should occur without discussion with the protocol team.

Dose reduction of SOF or LDV/SOF will not be allowed in the study. If SOF or LDV/SOF are stopped for toxicity, they should not be restarted. **For participants receiving SOF+RBV for whom SOF has been stopped, RBV should also be**

stopped and the **participant** should complete the treatment discontinuation visit. **Under no condition should the participant remain on RBV monotherapy.**

All **participants** must complete the PTx week 2, 4, 8, 12, and 24 visits. For **participants** who have completed the treatment discontinuation visit, the PTx week 2, 4, 8, 12, and 24 visits will be scheduled from the date of the last dose of study treatment.

Participants who meet any of the following laboratory criteria should stop treatment with SOF+RBV **or** LDV/SOF:

- Confirmed elevation of ALT and/or AST >3 x values measured upon study entry
- Confirmed direct bilirubin 3 x ULN and > 2.0 mg/dL
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with SOF **or** LDV/SOF

7.2 Pregnancy

Pregnancy will result in immediate discontinuation of the study medications and initiation of counseling regarding the teratogenicity of RBV **if in Cohort 1 and lack of information of safety in pregnancy with LDV/SOF if in Cohort 2**. **Participants** who become pregnant while on study will be followed on study/off treatment until study completion. A visit 6 months following the end of pregnancy will be conducted for evidence of AEs in the **participant** and infant, and an outcome CRF will be completed.

In Cohort 1, male participants whose partners become pregnant will undergo treatment discontinuation and remain on study for continued followup until the end of the study. They will receive counseling on RBV teratogenicity and the same followup visit at 6 months after their partners' delivery as outlined for pregnant women. **This same risk of teratogenicity is not seen with LDV/SOF, thus pregnancy of female partner in Cohort 2 is not an indication for treatment discontinuation.**

In Cohort 1, participants who become pregnant while taking study treatment or within 6 months after discontinuing study treatment and male **participants'** sexual partners who become pregnant during this time will have their pregnancies reported to the Ribavirin Pregnancy Registry (www.RibavirinPregnancyRegistry.com). **In Cohort 2, a female participant who becomes pregnant while taking the study treatment will have her pregnancy reported to the sponsor.**

If a female **participant** or female partner of a male **participant** has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF at the end of the pregnancy.

The intrapartum complications and/or pregnancy outcome will be recorded on the CRFs. If applicable, pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052. (For studies conducted at sites outside the US, report to The Antiretroviral Pregnancy Registry Fax: 44-1628-789-666 or 910-246-0637, Phone: 910-679-1598.)

7.3 HCV Virologic Response-Based Stopping Criteria

The following on-treatment HCV virologic response-based treatment stopping criteria will be utilized for all **participants**:

- Confirmed increase in HCV RNA \geq LLOQ if HCV RNA previously declined to $<$ LLOQ (detected or not detected)
- Confirmed $\geq 1 \log_{10}$ IU/mL HCV RNA on-treatment increase from nadir
- Confirmed HCV RNA \geq LLOQ at week 8 visit (in 12-week course of therapy)

Confirmation will be required for all stopping criteria and should be performed as soon as possible but within 2 weeks after determination of initial observation (see HCV VF Confirmation in section 6.1).

HCV RNA measurement to confirm treatment failure will be performed in real time at the designated VSL and the results will be provided to the site investigators within 2 weeks of specimen receipt. If treatment failure is confirmed, then all study treatment should be stopped. However, **participants** should be followed as per section 6.2.4.

Virologic evidence of relapse, defined as HCV RNA undetectable ($<$ LLOQ TND) at end-of-treatment but HCV RNA quantifiable (\geq LLOQ) during followup, will require confirmation and should be performed in real time at the designated VSL as soon as possible but within 2 weeks after determination of initial observation and the results will be provided to the site investigators within 2 weeks of specimen receipt.

7.4 HIV-1 Treatment Failure

In this study, HIV-1 viral breakthrough is defined as follows (only applies for **participants** on ART):

- Among **participants** with unquantifiable HIV-1 RNA at study entry, a confirmed increase to ≥ 200 copies/mL at any time after study entry.
- Among **participants** with quantifiable HIV-1 RNA at study entry, a confirmed increase of ≥ 200 copies/mL from study entry, at any time after study entry. (This is in consideration of possible change in HIV-1 RNA viral load status from screening to entry.)

The increase in plasma HIV-1 RNA should be confirmed with repeat local testing as soon as possible (not to exceed 4 weeks); see HIV VF Confirmation in section 6.1. For **participants** with confirmed HIV-1 viral breakthrough (≥ 200 copies/mL), a plasma specimen should be obtained and sent to the designated A5327 Virology Support

Laboratory (VSL) for evidence of HIV-1 drug resistance. Results will be reported back to sites in real-time from the designated A5327 VSL.

Clinical management of HIV-1 virologic breakthrough and treatment failure will be handled by local site investigators according to current HIV treatment guidelines and local standard of care. The A5327 protocol core team should be contacted before switching ART.

HCV medications should be continued unless safety events warrant the discontinuation of these medications, as outlined in Section 8.1 of the protocol.

These criteria only apply to **participants** currently on ARV treatment. They do not apply to **participants** meeting the ARV untreated parameters outlined in section 4.1.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation

- Drug-related toxicity (see section 7.1 Toxicity).
- Pregnancy in a female **participant**.
- **Pregnancy** in the female partner of male **participant (Cohort 1 only)**.
- HCV efficacy failure as defined in section 7.3.
- Significant protocol violation including noncompliance with study assessments.
- **Participant** request to discontinue for any reason.
NOTE: It is important to determine whether the treatment discontinuation is primarily due to an AE, lack of efficacy, or other reason.
- Requirement for prohibited concomitant medications (see section 5.4).
- Breastfeeding.
- Completion of treatment as defined in the protocol.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

8.2 Premature Study Discontinuation

- Request by the **participant** to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the **participant**.
- **Participant** judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the Study Monitoring Committee (SMC), ACTG, IRB, NIAID, Office for Human Research Protections (OHRP), any other government agency as part of their duties, investigator, or industry supporter.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This study will evaluate the efficacy and safety of a 12-week regimen of SOF combined with RBV (**Cohort 1**) and an 8-week regimen of LDV/SOF (**Cohort 2**) for the treatment of acute HCV infection among individuals coinfecting with HIV. Efficacy will be evaluated using SVR12 as the primary outcome measure. A true SVR12 rate of less than or equal to 60% will be considered as reasonably ruled out if the two-sided 90% CI for the rate is entirely above 60% (this is equivalent to showing that the rate is higher than 60% in a one-sided noninferiority test with a Type I error rate of 5%).

The threshold of 60% for the SVR12 rate was chosen based on a summary of nine acute HCV treatment studies in HIV-1 coinfecting **participants** identified in a recent report by the European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel [AIDS, 2011]. In this summary, 96 (60%) of 159 **participants** treated with PEG/IFN combined with RBV achieved SVR24 (i.e., the conventional definition of SVR evaluated at 24 weeks after stopping treatment).

The sample size of 17 **participants** for the evaluation of the 12-week **SOF+RBV** regimen in **Cohort 1** was chosen to provide good power to show noninferiority with respect to the 60% threshold assuming that the underlying true SVR12 rate is 90%. **In part because of the lower than expected observed SVR12 rate for SOF+RBV in Cohort 1**, the sample size of 27 **participants** for the evaluation of the 8-week **LDV/SOF** regimen in **Cohort 2** was chosen to provide good power to show noninferiority with respect to the same 60% threshold assuming that the underlying true SVR12 rate is 85%.

The primary analysis will be ITT and will include all **participants** who start study treatment. In this ITT analysis, the standard definition of SVR12 will be used, ie, ignoring whether or not a **participant** discontinued study treatment early and considering **participants** who are lost to followup or otherwise unevaluable for SVR12 as not meeting the definition for SVR12. An important secondary analysis will include **participants** who are evaluable for SVR12 but exclude **participants** who prematurely discontinue study treatment for nonvirologic reasons ("completer" analysis). To ensure that the "completer" analysis is also well-powered, if a **participant** is discontinued from the study treatment for nonvirologic reasons or is not evaluable for SVR12 while enrollment is ongoing to the same cohort, then an additional **participant** may be enrolled to that cohort, up to a maximum enrollment for the study as a whole of 50 **participants**.

The study has not been designed to be well powered to compare the 12-week **SOF+RBV** and 8-week **LDV/SOF** regimens.

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

- 9.2.1.1 SVR12 defined as HCV RNA undetectable (<LLOQ TND) of the assay at 12 weeks after date of last dose of study treatment. The 12 week measurement will be the measurement obtained closest to 84 days (ie, 12*7 days), within the window 79 to 112 days inclusive. If a **participant** has no HCV RNA measurement within this window, then the **participant** will be considered as having detectable HCV RNA at 12 weeks unless the preceding and subsequent HCV RNA measurements are both undetectable (<LLOQ TND).
- 9.2.1.2 Occurrence of Grade ≥ 2 AE (diagnosis, sign, symptom or laboratory abnormality), SAE according to ICH criteria, or treatment-limiting AE (ie, an AE reported as the reason for permanent discontinuation of study treatment). Any event occurring after initiation of study treatment through to 28 days after date of last dose of study treatment will be included (except that an event that is ongoing at the same grade from before start of study treatment will be excluded).

9.2.2 Secondary Outcome Measures

- 9.2.2.1 HCV RNA undetectable (<LLOQ TND) at 1, 2, 4, 8 and, for the 12-week regimen, 12 weeks after starting study treatment. Measurements will be assigned to these times within windows of 4 to 10, 11 to 17, 21 to 42, 49 to 70, and 77 to 98 days, inclusive, respectively. If there is more than one measurement within a window, then the measurement closest to the targeted time will be used. If there is no measurement within a window, then the **participant** will be considered as having detectable HCV RNA at the targeted time, unless both the preceding and succeeding measurements are undetectable (<LLOQ TND).
- 9.2.2.2 HCV RNA undetectable (<LLOQ TND) at 2 (SVR2), 4 (SVR4), 8 (SVR8), and 24 (SVR24) weeks after last dose of study treatment. The windows for these measurements will be 9 to 22, 23 to 50, 51 to 78, and 161 days onwards. If there is more than one measurement within a window, then the measurement closest to the targeted time will be used. If there is no measurement within a window, then the **participant** will be considered as having detectable HCV RNA at the targeted time, unless (for weeks 4 and 8) the preceding and subsequent HCV RNA measurements are both <LLOQ TND.
- 9.2.2.3 To evaluate virologic evidence of relapse, defined as HCV RNA undetectable (<LLOQ TND) at end-of-treatment but HCV RNA quantifiable (\geq LLOQ) during followup, will require confirmation and

should be performed as soon as possible but within 2 weeks after determination of initial observation.

- 9.2.2.4 Development of SOF **or** LDV-associated resistance mutations. The set of mutations to be considered will be defined at the time of analysis based on information from other studies available at that time.
- 9.2.2.5 Occurrence of the AEs detailed in section 9.2.1.2 by type of event.
- 9.2.2.6 Change in HIV-1 RNA from last measurement prior to start of study treatment to each subsequent scheduled HIV-1 RNA measurement time: for **participants** on ART at study entry, these will be categorized as changes from <50 copies/mL to ≥50 copies/mL, or vice versa; for **participants** not on ART at study entry, quantitative change in log₁₀ HIV-1 RNA will be considered. Windows for measurements to be included and the algorithm for selecting measurements within each window will be as described for HCV RNA measurements above.
- 9.2.2.7 Change in CD4+ cell count from last measurement prior to start of study treatment to each subsequent scheduled CD4+ cell count measurement time. Windows for measurements to be included and the algorithm for selecting measurements within each window will be as described for HCV RNA measurements above.
- 9.2.2.8 Measures of adherence: for each of SOF and **RBV (in Cohort 1) or LDV/SOF (in Cohort 2)** at each visit: (a) self-reported adherence as measured by whether or not a **participant** reports having taken all doses; and (b) proportion of doses taken since the previous visit as determined by pill count.
- 9.2.2.9 Immune parameters: changes in magnitude of induction of ISGs by Nanostring, changes in IP-10 levels, and changes in T cell function (CD4+ proliferative and CD8 CTL assays) at end of treatment and end of followup compared to study entry. Analysis will be performed as a function of IL28B genotype.

9.3 Randomization and Stratification

There is no randomization or stratification in this study. The study includes two cohorts of **participants**; these cohorts will be enrolled sequentially.

9.4 Sample Size and Accrual

In this section, the selection of sample size is described **separately for Cohort 1 and for Cohort 2**. Note that the study has been designed to allow for small increases in sample size from 17 in **Cohort 1** and 27 in **Cohort 2**, if some **participants** prematurely discontinue study treatment due to nonvirologic reasons or are not evaluable for the

primary outcome measure of SVR12. The rationale for the increase in sample size is then to provide similar power in the “completer” analysis (described in section 9.1) as there would be in the primary ITT analysis, if no additional **participants** are enrolled (ie, based on 17 **participants** in **Cohort 1** and 27 **participants** in **Cohort 2**). In addition, if there are **participants** in screening at the time that first cohort meets its accrual goal, or at the time that the second cohort meets its accrual goal, then these **participants** may complete screening and enroll in the study provided that this can be achieved within 30 days (the site must provide the patient ID for these **participants** to the study team to enable enrollment). Also, if a **participant** is enrolled in the study and does not start study treatment, then the **participant** will not be followed and may be replaced if enrollment is still ongoing.

Cohort 1 enrolled 17 participants in about 4.5 months. It is therefore anticipated that it will take about 7 months to enroll 27 participants in Cohort 2.

9.4.1 Sample size of 17 participants in Cohort 1 receiving the 12-week SOF/RBV regimen

Version 1.0 of the protocol provided detailed justification for the sample size of 17 participants for Cohort 1. In brief, the sample size of 17 participants for the first cohort has been chosen to provide good power to show with reasonable certainty that the underlying true SVR12 rate is greater than 60%. This **was to** be established if the two-sided 90% CI for the rate **was** entirely above 60% (this is equivalent to showing that the rate is higher than 60% in a one-sided noninferiority binomial test with a Type I error rate of 5%). Assuming that the true SVR12 rate **was** 90% among those treated with the 12-week regimen, 17 **participants were** needed to provide 90% power to establish this. With a sample size of 17 **participants**, the CI for the true SVR12 rate **would** be entirely above 60% if 14 or more of the 17 **participants achieved** SVR12.

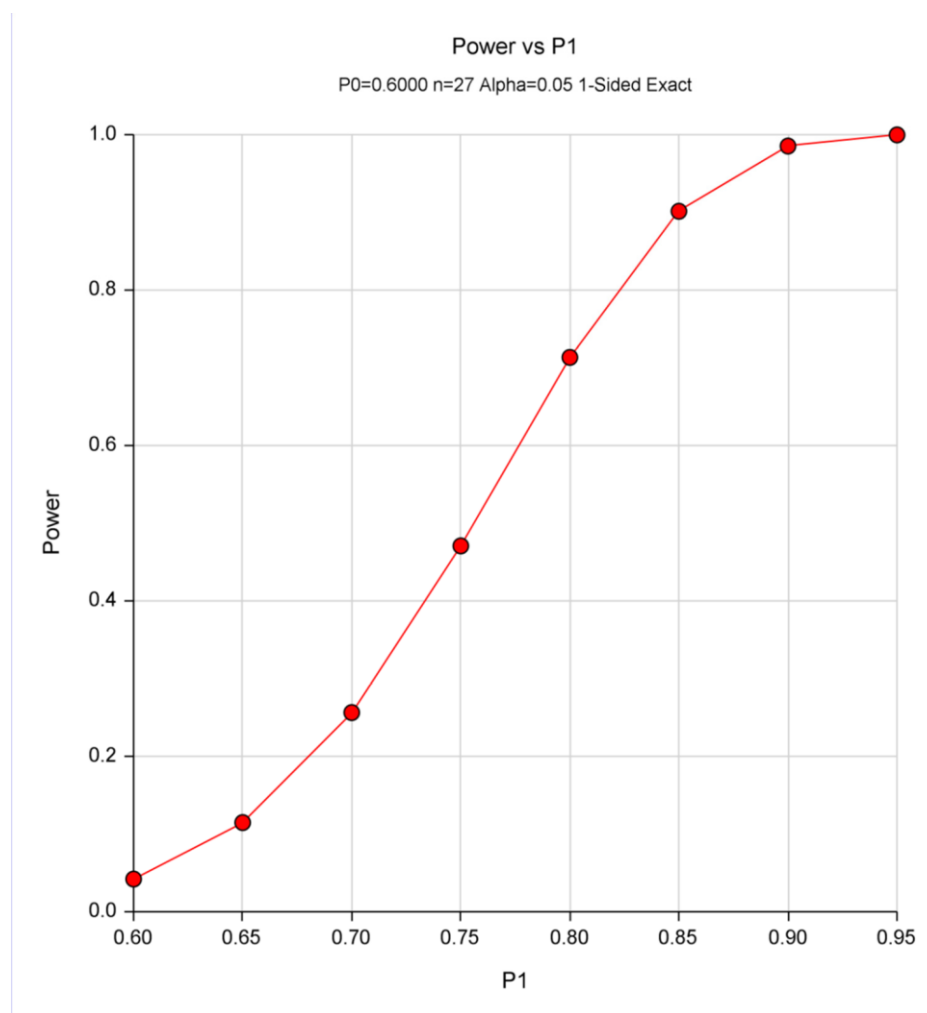
9.4.2 Sample size of 27 participants in Cohort 2 receiving the 8-week LDV/SOF regimen

A larger sample size has been chosen for the second cohort of **participants** than for the first cohort to allow for the possibility that the underlying true SVR12 rate **is 85%**. Specifically, the sample size of 27 **participants** for the second cohort has been chosen to provide 90% power to show with reasonable certainty that the underlying true SVR12 rate is greater than 60%, assuming that this true rate is actually 85%.

In this sample size calculation, no adjustment is needed for loss to followup because, by definition, such participants are assumed not to be SVR12. However, it is important to note that the study team feels that the lost to followup rate will be very low, specifically less than 5%. There is support for this from Cohort 1, in which no participants were lost to followup, and from an ACTG acute HIV infection study, A5217, in which the lost to followup rate within 24 weeks of enrollment was 4.6% (6 of 130

participants). The study team considers an underlying true SVR12 rate of 85% to be plausible based on the results of studies in chronically infected participants (see section 2.2.3.1).

The figure below shows the study's power to establish noninferiority with respect to the 60% threshold in the second cohort of 27 **participants** for a range of values of the underlying true SVR12 rate (expressed as a proportion, P_1 , in the figure). As can be seen the study has reasonable power ($\geq 80\%$) for true underlying SVR12 rates greater than about 82%.



The table below also shows two-sided **exact Blyth-Still-Casella (BSC)** 90% CIs for potential observed SVR proportions for 27 enrolled **participants** in the 8-week treatment arm. **With a sample size of 27 participants, the CI for the true SVR12 rate will be entirely above 60% if 21 or more of the 27 participants achieve SVR12.**

Observed SVR12 Rate	90% CI for True SVR12 Rate
85% (23/27)	(71%, 93%)
81% (22/27)	(65%, 90%)
78% (21/27)	(62%, 90%)
74% (20/27)	(58%, 85%)
70% (19/27)	(54%, 84%)
67% (18/27)	(50%, 80%)

9.5 Monitoring

The study team will monitor accrual, retention, and completeness of key laboratory measurements (HCV RNA and HIV-1 RNA). In addition, standard ACTG SDAC AE reports and summaries of changes in HIV-1 RNA will be reviewed by the study team including the DAIDS Medical Officer every 3 months. The formats of these reports will be outlined in the Study Monitoring Plan, developed by the Statistical and Data Management Center (SDMC) and reviewed by the study team prior to study enrollment. Information about SVR rates will not be reviewed on a routine basis by the study team.

This study **is** also monitored by the ACTG Hepatitis **Study Monitoring Committee (SMC)**. **For Cohort 2, because of a hypothetical risk of renal toxicity due to increased TFV exposure in participants taking COBI or taking TDF in combination with a boosted HIV PI, the SMC will review the study when 5 participants taking these regimens have completed 4 weeks of study treatment, and at least annually after the first participant is enrolled for as long as participants are taking study treatment.** The reviews will include information about accrual, retention, completeness of key laboratory measurements (HCV RNA and HIV-1 RNA), AEs, changes in HIV-1 RNA, and efficacy (SVR4, SVR12, SVR24 rates and changes in HCV RNA).

It is not intended that the SMC terminate the study early if the SVR12 rate is very high. The SMC may, however, recommend early termination if the SVR4 rate or the SVR12 rate is unacceptably low, for example if the 90% CI is entirely below 60% (the confidence intervals will not be adjusted for interim analyses). The SMC may also make recommendations about modification or termination of the study based on safety considerations or because of poor accrual.

9.6 Analyses

A detailed Statistical Analysis Plan (SAP) **was** developed after Version 1.0 of the protocol **was** finalized. The following provides a brief summary of analyses that will address the primary and key secondary objectives.

The primary efficacy objective will be addressed by estimating the proportion of **participants** within a cohort who achieve SVR12 in ITT analysis. The denominator will be the number of **participants** in a cohort who start study treatment. A two-sided 90% CI will be calculated for proportion using the BSC method for binomial outcomes. If this confidence interval is entirely above 60%, then it will be concluded that there is reasonable evidence that the underlying true SVR12 rate is greater than 60% (ie, noninferior to 60%). An important secondary analysis will use similar methods to evaluate the primary outcome measure in the “completer” analysis (defined in section 9.1). Secondary efficacy objectives (proportions of **participants** achieving HCV RNA undetectable (<LLOQ TND) during study treatment and achieving SVR4, SVR8, and SVR24) will be addressed in a similar way. Possible predictors of response (adherence, HCV genotype, host IL28B genotype, etc.) will be evaluated using univariate exact logistic regression; multivariate models will also be considered if there are sufficient numbers of events (eg, of **participants** not achieving SVR12). Descriptive statistics will be used to describe adherence measures at each study visit.

The primary safety objective will be addressed by estimating the proportion of **participants** who have one of the defined AEs. The denominator will be the number of **participants** in a cohort who are dispensed study treatment. A two-sided 90% confidence interval will be calculated for each proportion using the BSC method for binomial outcomes. Descriptive tables summarizing types of AEs, grades of events, and the number of persons experiencing each type/grade of event will be provided. Descriptive tables will also be provided for the number of **participants** discontinuing study treatment early, categorized by the reasons for discontinuation. Changes in HIV-1 RNA and CD4+ cell count at each scheduled measurement time will be described separately for **participants** on versus not on ART at study entry.

Results from **Cohort 1** may be presented publicly, for example at a conference or in a published manuscript, while followup of **participants** enrolled in **Cohort 2** is ongoing. The final analysis of data from **Cohort 2** will be undertaken when all **participants** have completed 24 weeks of followup after discontinuing study treatment and data are available. However, a preliminary analysis may be undertaken after all **participants** in **Cohort 2** have completed 12 weeks of followup after discontinuing study treatment and data are available if this facilitates submission of an abstract to a conference for presentation of study results.

10.0 PHARMACOLOGY PLAN

Nucleos(t)ide analogs are fundamental components of the treatment for HCV, yet there are limited data on the pharmacology of the active form of these drugs, the intracellular triphosphate, in vivo. Data from the SPARE trial [Osinusi A, 2013] of SOF/RBV in 60 individuals with HCV genotype 1 disease found intracellular RBV concentrations were associated with treatment response and the development of anemia [Rower, J Antimicrob Chemother, accepted 2015]. Analysis of intracellular SOF pharmacokinetics from the SPARE study is ongoing. The PK of these drugs

may therefore be important predictors of SVR vs. relapse in A5327. Furthermore, traditional tools to monitor adherence (eg, pill counts, self-report, refill histories, etc.) have shortcomings and consistently over-estimate drug taking behavior. RBV has a long half-life of 10-12 days [Wu, 2015; Rower, J Antimicrob Chemother, accepted 2015]. Thus, it can be used as a quantitative objective measure of cumulative drug dosing (ie, adherence). These data may be instrumental in evaluating response rates (as it was for TDF for pre-exposure prophylaxis). Intracellular concentrations of SOF metabolites (GS-331007 triphosphate or “007-TP”) may also predict response and reflect cumulative drug dosing. A5327 offers a unique opportunity to evaluate the pharmacokinetic-dynamic and adherence-response associations for nucleos(t)ide analogs. Additionally, though we are not planning to investigate this a priori to limit costs and because there is no pharmacologic reason to suspect an interaction, we will also have the potential to investigate unexpected drug-drug interactions with ARV agents.

Assessing the Potential Effects of LDV/SOF on TFV Concentrations in Those on RTV-Boosted HIV Protease Inhibitors or on COBI-Containing Regimens.

Healthy volunteer studies indicate that LDV/SOF in combination with ritonavir-boosted PIs, increases TFV concentrations by 47-64% [German P, CROI 2015 abstract 82]. These data were not available at the time of ION-4 enrollment and thus boosted HIV PI regimens were excluded from the study. It is therefore unknown if this increase in TFV exposure has clinical relevance. A5327 provides an opportunity to investigate the clinical significance of increased TFV exposures in the setting of concomitant dosing of LDV/SOF, ATV/r or DRV/r, and TDF. Due to similar concerns of increased TFV exposure in the setting of COBI usage and an increase in TFV AUC similar to that seen in PI/r based regimens A5327 also provides the opportunity to investigate the clinical significance of TFV exposures in the setting of concomitant dosing of LDV/SOF, COBI, and TDF.

10.1 Pharmacology Objectives

10.1.1 Develop a population PK model for ribavirin to estimate RBV PK in persons with HIV-1 and acute HCV and evaluate covariates, including concomitant administration of selected ARV drugs which may affect RBV PK.

10.1.2 Develop a population PK model for LDV and SOF metabolites to estimate PK in persons with HIV-1 and acute HCV and evaluate covariates, including concomitant administration of selected ARV drugs which may affect LDV and SOF metabolite PK.

10.1.3 Determine the associations between adherence assessed using traditional measures (eg, self-report and pill counts) and drug concentrations.

10.1.4 Investigate PK-PD relationships for RBV, LDV, and SOF metabolites.

10.1.5 Compare TFV pharmacokinetics in participants on RTV-boosted PIs or COBI with TDF before and after the addition of LDV/SOF.

10.2 Pharmacology Study Design

Plasma **and** DBS will be obtained from all **participants** prior to initiation of SOF+RBV **or** LDV/SOF, at entry, weeks 1, 2, 4, 8, and 12 following SOF+RBV **or** LDV/SOF initiation (weeks 8 and 12 only in those who receive 12 weeks of treatment), HCV VF and HIV-1 VF Confirmation and premature discontinuation visits, and at weeks 2, 4, 8, and 12 post-treatment. Samples are collected prior to treatment initiation and after discontinuing treatment in the event there is a need to retrospectively evaluate the potential for ARV drug interactions or adherence, but these samples will not be analyzed a priori to limit costs.

Plasma RBV and intracellular ribavirin triphosphate concentrations will be determined using validated LC/MS/MS methods, respectively. The HPLC-UV method used to quantify ribavirin in plasma has a linear range of **0.1-10 mcg/mL**. The LC/MS/MS method used to quantify ribavirin triphosphate has a linear range of 0.5-200 pmol/sample [Jimmerson LC, 2015].

Plasma LDV, GS-331007 and intracellular 007-TP concentrations will be determined using validated LC/MS-MS methods. The LC-MS/MS method used to quantify 007-TP has a linear range of 50-50000 fmol/sample [Rower, submitted to Analytical and Bioanalytical Chemistry, 2015].

10.3 Primary and Secondary Data, Modeling, and Data Analysis

To address **objectives 10.1.1 and 10.1.2**, nonlinear mixed effects models will be fit to the **drug** concentrations to estimate the PK of **the drugs** in persons with HIV-1 acutely infected with HCV. After the base model is established, the effect of covariates such as age, race, gender, and concomitant ARV on PK will be assessed.

To address objective 10.1.3, Pearson correlations will be used to evaluate the association between self-reported adherence and drug concentrations and pill counts and drug concentrations.

To address objective **10.1.4**, **logistic regression will be used to** investigate the relationships between **drug concentrations and SVR and RBV PK and anemia** (hemoglobin <10g/dL).

Objective 10.1.5 will be addressed if there is a signal for renal toxicity in individuals receiving RTV-boosted HIV PIs. For this objective, TFV levels will be compared before and after the addition of LDV/SOF in those receiving RTV-boosted HIV PIs using paired t-tests.

10.4 Anticipated Outcomes

Through the pharmacology objectives of this study, we will determine the PK of RBV, **LDV, and SOF metabolites** in persons with HIV-1 acutely infected with HCV. We will

also evaluate the effect of covariates such as age, race, gender, and concomitant ARV on the PK of these agents. **We will determine the association between traditional measures of adherence (self-report and pill count) and adherence determined using drug concentrations.** We will explore relationships between **RBV, LDV, and SOF metabolites with SVR** and RBV plasma and intracellular PK and the development of anemia. **If the need arises, we will assess changes in TFV concentrations with the addition of LDV/SOF in individuals receiving RTV-boosted PIs.** These data will guide optimal use of **SOF+RBV or LDV/SOF in the setting of acute HCV.**

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each **participant**. **Participants** must not be identified by name on any CRFs. **Participants** will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual **participant** records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study **participants**, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NIAID, the OHRP, and the industry supporter or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study **agents** for which expedited reporting are required are ribavirin (RBV), sofosbuvir (SOF), and **fixed dose combination of ledipasvir/sofosbuvir (FDC LDV/SOF)**.

11.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), must be used and is available on the DAIDS RSC Web site at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the time of enrollment of the study **participant** until the study **participant** completes study followup.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (**Appendices II and III**) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the **participant**. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the **participant**, and this fact will be documented in the **participant's** record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain **participant** confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the **participant**, except as necessary for monitoring by the ACTG, IRB, NIAID, OHRP, other government agencies as part of their duties, or the industry supporter or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB, NIAID, OHRP, other government agencies as part of their duties to ensure that research **participants** are protected, or the industry supporter.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

14.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please

refer to instructions detailed in the International Air Transport Association (IATA)
Dangerous Goods Regulations.

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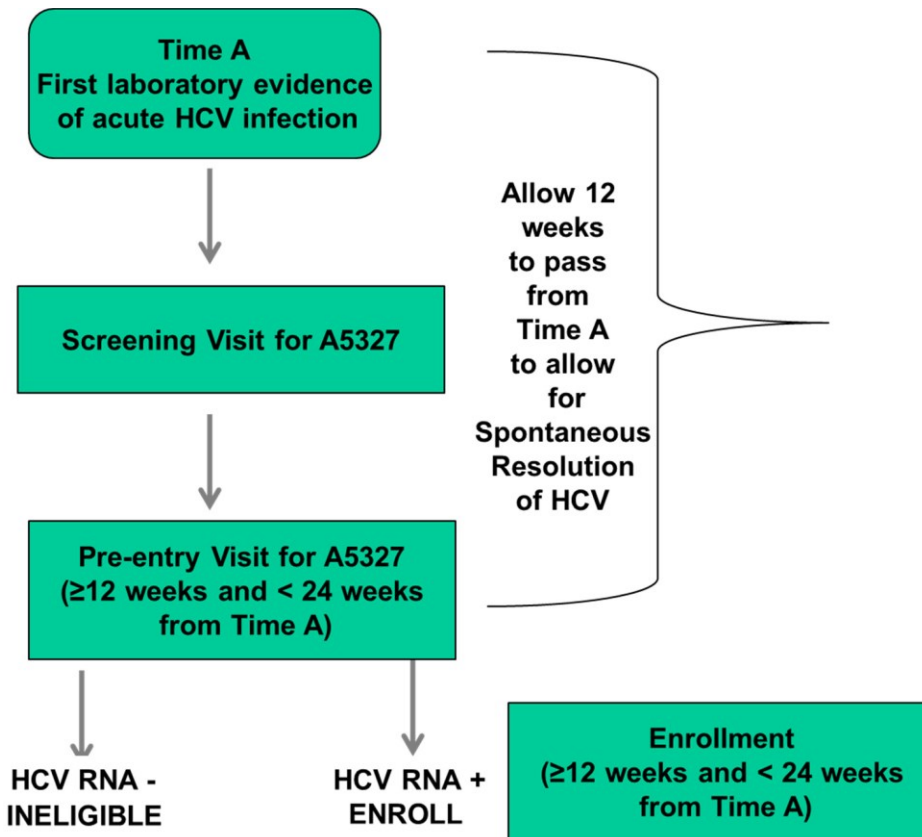
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APPENDIX I: SCREENING FLOW CHART FOR ACUTE HCV INFECTION



APPENDIX II

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT **FOR COHORT 1**
For protocol: A5327

FINAL Version 1.0, 01/02/14: Sofosbuvir Plus Ribavirin Without Interferon For Treatment of Acute HCV in HIV-1 infected Individuals (SWIFT-C)

SHORT TITLE FOR THE STUDY: A5327/SWIFT-C FINAL Version 1.0, 01/02/14, SOF/RBV Without IFN For Treatment of Acute HCV Infection

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS) and you have also recently been infected with the hepatitis C virus (HCV, a virus that affects the liver). This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

People who are recently infected with HCV have a great chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being infected. This study is being done to see if a new drug can replace one of the old drugs to provide a safer, more effective, and better tolerated treatment for new HCV infection. The name of this new drug is sofosbuvir (SOF), and it will replace pegylated-interferon alfa (PEG-IFN, a drug given as a weekly injection under the skin). SOF will be given in combination with ribavirin (RBV), a drug approved by the Food and Drug Administration (FDA).

SOF has been approved by the FDA for the treatment of chronic HCV in people who do not have HIV. It is also currently being studied in people with HIV and chronic HCV.

All participants in this study will be monitored while on treatment at weeks 1, 2, 4, 8, and 12. All participants will be evaluated for a sustained virologic response (SVR) (undetectable HCV RNA levels) 1, 2, 4, and 8 (for the 8-week regimen) or 12 (for the 12-week regimen) weeks after starting study treatment. After completing treatment, all participants will be evaluated for a SVR 2, 4, 8, 12, and 24 weeks after the end of treatment.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 44 people (men and women age 18 years and older) will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?



You will be in this study for approximately 36 weeks.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study, you will continue taking your current anti-HIV drugs if you are receiving them. If you are not currently on HIV medications and your provider does not think you need HIV medications during the study that is also acceptable. You will be assigned to either group 1 or group 2, as shown below. You will take SOF (a pill taken once daily by mouth with food) and RBV (pills taken twice daily by mouth with food and at a dose based on your weight) until the end of treatment. You will be given the medications at your study visits to take home, and you will need to store the medications in a safe place at room temperature. Following the end of the 12-week treatment and based on the HCV RNA results of those who were enrolled in group 1, the length of therapy may be shortened in group 2, as shown below.

Study Group	Study Drugs	SVR Rates	Time on Study Drugs	End of Treatment
Group 1	SOF+RBV	SVR (week 4) results available from subjects	12 weeks	No study treatment – continue study followup for 24 weeks

At week 4, the study team will look at SVR results. Group 2 will depend on what the results show. We will look to see if SVR is met at week 4.

Study Group	Study Drugs	SVR Rates High Enough?	Time on Study Drugs	End of Treatment
Group 2	SOF+RBV	IF YES 	8 weeks	No study treatment – continue study followup for 24 weeks
Group 2	SOF+RBV	IF NO 	12 weeks	No study treatment – continue study followup for 24 weeks

Everyone who enters the study will take SOF and RBV, which will be given for free by the study. Anti-HIV drugs will not be provided by the study. Note that if you stop taking SOF, you must also stop taking RBV.

While you are in this study, you will need to be seen in the clinic about 11 times during the study. The study staff will tell you about how long each visit could be. You may need to come to the clinic if you have side effects or if you switch or take new anti-HIV drugs. More information about the study tests is given below. During the study, you will get the results from any routine tests that are done during the study when they are available.

You must fast for the screening, week 4 on-treatment, end of treatment (week 8 or 12), week 12 post treatment, and early treatment/study discontinuation visits. **You may also have to fast for the entry visit; the study staff will inform you if you must fast for the entry visit.** (Fasting means that you should not eat or drink anything for at least 8 hours before your visit. You may only drink water and take your prescription medications during this time. If your medications require food, the study staff will talk to you about how you should take your medications.) The study staff will remind you to fast before each of these study visits. If you do not fast before these visits, you will be asked to come back later for these tests after fasting.

If you do not enroll into the study

If you decide not to take part in this study or if you do not qualify to take part in this study, we will still use some of your information. As part of the screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ T-cell count, viral load) information is being collected from you so that ACTG researchers may see if there are patterns or common reasons why people do not join a study.

Required Tests

Your blood will be drawn from a vein in your arm and used to measure your HCV and HIV viral load (the amount of HCV and HIV in your blood) and genotype (genetic makeup of the virus), to measure your CD4+/CD8+ cell counts (these are cells in your blood that fight infection), to measure levels of certain hormones (hormones are chemicals in your blood), and for routine safety tests and metabolic tests (to test how your body uses the food that you eat). You will be told the results of these tests when they become available.

Some of your blood will also be stored (with no information that will identify you) and used for future HCV/HIV resistance tests required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications. In addition, some of this blood will be used to understand how the drugs interact with your body and how your body responds to the drugs.

Any remaining blood will be stored for future testing required by the study.

Additional Tests

If you agree, your blood will be drawn and used for future testing. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your blood used for future ACTG-approved research. You may change your mind at any time and your samples will be destroyed.

_____ YES _____ NO

Genetic (the message in your DNA) testing

If you agree, your blood will be drawn and used to examine different genes (pieces of your DNA). Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your blood used for ACTG-approved genetic testing. You may change your mind at any time and your samples will be destroyed.

_____ YES _____ NO

Optional Tests

If you agree, any blood left over after all required study testing is done may be stored (with no information that will identify you) and used for future ACTG-approved research. These blood samples may be stored for an unknown period of time. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your leftover blood used for future ACTG-approved research. You may change your mind at any time and reasonable efforts will be made to destroy your samples, though this may not always be possible.

_____ YES _____ NO

A5327 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Study Schedule

Evaluation or test	Screen	Pre-Entry	Entry	Post-Entry Visits			Other Visits	Early discontinuation
				On-treat-ment Visits	End of treatment	Off-treat-ment Visits		
Consent	✓							
Clinical assessments	✓		✓	✓	✓	✓		✓
ECG	✓							
Samples collection & laboratory testing	✓	If required	✓	✓	✓	✓	✓	✓
Urine sample			✓					
Pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓

Evaluation or test	Screen	Pre-Entry	Entry	Post-Entry Visits			Other Visits	Early discontinuation
				On-treat-ment Visits	End of treatment	Off-treat-ment Visits		
Pharmacokinetic (PK) studies			✓	✓	✓	✓	✓	✓
Pregnancy prevention counseling			✓	✓	✓	✓		✓
Adherence assessments				✓	✓			✓
Study drugs distribution and storage			✓	At week 4	At week 8 for groups 1 and 2 on 12-wk tx schedule			

II. Description of Study Visits

Screening

After you have read and signed the consent form, you will be asked questions about your health, medical history, and medication history. You will have several tests, including blood tests, to make sure that you qualify to join the study. Some of the blood taken will be shipped to a testing lab. Your new HCV infection and how long you've been infected will be confirmed. You must come to the visit fasting. If you are not fasting within the past 8 hours before this visit, you will be asked to come back fasting. Also, an electrocardiogram (ECG) will be done at this visit.

If you are a female, you will have blood or urine taken for pregnancy testing.

Pre-entry

You may be asked to return to the study clinic to have a repeat HCV viral load to confirm that you still have the infection. If you do still have the infection, you will come back for the entry visit. If you do not have evidence of ongoing infection, you will not enter the study. You will be referred back to your doctor for followup to ensure the virus does not come back. If you are a female, you will have blood or urine taken for pregnancy testing.

Entry

When all of the results from your screening tests are available, you will come back to the clinic to have a few tests done before starting the study. You will have urine and blood samples collected for routine safety tests. If you are a female, you will be asked to provide blood or urine sample for pregnancy testing. **You may need to come to the clinic fasting for this visit (fasting means that you should not eat or drink anything for at least 8 hours before your visit). The study staff will inform you before the entry visit if you have to be fasting.** If you are not fasting within the past 8 hours before this visit, you will be asked to come back fasting.

At this visit, you will get your study drugs. The study staff will give you enough study drugs to last until the week 4 visit. You should take RBV and SOF with food. At each visit, you must return any remaining study drug from the previous visit. If you forget to take SOF at the correct time, it may be taken later in the day; however, no more than a single daily dose (400 mg dose) of SOF should be taken on any calendar day. You should never cut or split your study medications. If you miss a dose of RBV, then you should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then you should skip the missed dose, and then you should go back to your normal dosing schedule. You do not double the next dose in order to "make up" what has been missed. You will have an extra evaluation (pharmacokinetic [PK] testing) done at the entry visit. This evaluation is described below.

Post-entry visits

You will be seen at treatment weeks 1, 2, 4, 8, and 12 (unless treatment is only planned for 8 weeks total) AND at post-treatment weeks 2, 4, 8, 12, and 24 after taking the last dose of study drugs. These visits will last about 1-1½ hours each.

If you are a woman, you will be asked to provide blood or urine sample for pregnancy testing.

Other visits

During the study, you may have to come back to the clinic for extra visits for testing of any lab results that are not normal, or to followup on a specific side effect or symptom.

Virologic Failure Confirmation

If laboratory tests show there is evidence of virologic failure (which is detectable HCV when you were previously undetectable or your virus has not gone down as quickly as expected), you will be asked to return to the clinic to confirm your lab results. If virologic failure is confirmed, you will then complete an early discontinuation study visit as described below.

Early discontinuation

There are two types of discontinuation (stopping study treatment or leaving the study early) in which you will be asked to come to the clinic for an extra visit in a fasting state.

1. Stop study treatment early

You or your doctor may decide to stop the study medication that you began at entry.

If you must stop taking the study medication early, the study doctor may ask you to stay in the study and come in for some tests.

2. Leave study early

You or your doctor decides that you will no longer stay in the study or you are notified the study is stopped early. You will be asked to complete some evaluations before being taken off the study.

III. Description of Study Evaluations

Consent

After you read the consent form and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be tested to see if you qualify for the study.

Clinical Assessments

You will have the following clinical evaluations in this study:

Physical examination

You will have a physical exam. The study staff will check the different systems in your body such as head, neck, eyes, ears, nose, throat, mouth and tongue, chest (excluding breasts) for respiratory, heart for cardiovascular, abdomen, skin, hair, nails, and muscles and joints. The study staff will also check your vital signs such as temperature, pulse, blood pressure, and respiratory rate, and your height and weight will be recorded.

Medical and medication history

You will be asked questions about your health and about any medicines you have taken or are taking now. Once you are on treatment, you will be asked about any signs or symptoms that you are experiencing and any changes in other medications that you have had since your last visit.

Electrocardiogram

You will have an electrocardiogram (ECG) done. An ECG is a test to measure the heartbeat. An ECG machine will be used to do an electrical tracing of your heart that can show how hard it is working. You will have to lie very still for at least 5 minutes while the ECG is being done.

Sample collections and laboratory testing

You will have the following samples collected and tested in this study:

Blood collected

Blood will be taken from a vein in your arm for various tests during the study. Approximately 144 mL (10 tablespoons) of blood will be drawn during any study visit. These may include: routine safety lab tests such as kidney and liver function, HIV viral load (a test that shows how much HIV is in your blood), CD4+/CD8+ counts (a test that shows how many infection-fighting cells you have in your blood), HCV viral load (a test that shows how much HCV is in your blood).

You will be asked to fast before some of the visits. This means that you should not eat or drink anything except prescription drugs and water for at least 8 hours before the visit.

Resistance testing

Blood will be drawn and stored for future HCV/HIV resistance testing that is required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications.

Genetic testing

If you agree blood will be drawn for testing your genes (pieces of your DNA) to understand if you naturally were born with a better or worse chance of responding to the medications. Some of your blood cells will also be tested to see if your responsiveness to the therapy is associated with different genes related to IFN use. An IFN is an antiviral compound that is produced in response to many types of infections. You will not receive the results of these studies because they will be done in the future.

PK Studies

Blood will be drawn to measure the levels of the study drugs in your blood and to understand how the drugs interact with your body and how your body responds to the drugs.

Urinalysis

Urine samples will be collected for routine safety tests.

Pregnancy test

If you are a woman, you will have blood or urine taken prior to study entry. After you enter the study, you will be asked to provide blood or urine samples for pregnancy testing.

Pregnancy prevention counseling

All participants, male and female, will be counseled on the risk of the study drugs in pregnancy and on how to prevent pregnancy.

Adherence assessments

You will be asked about how well you take your medications. The study staff will give you information and encouragement to help you take your medications as prescribed.

Study drugs distribution and storage

You will be given a 4-week supply of study medications at entry, week 4, and at week 8 (for a 12-week treatment). You will be asked to store the study medications as instructed in the medicine bottle label.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is cancelled.
- a Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC is an outside group of experts who monitor the study).
- your doctor thinks the study is no longer in your best interest.
- the site investigator thinks that you are at significant risk of failing to comply with the requirements of the protocol.

The study doctor may also need to take you off the study drugs without your permission if:

- you experience HCV treatment failure.
- you or a female partner of a male participant become pregnant.
- you are breastfeeding.
- continuing the study drugs may be harmful to you.
- you need a treatment that you may not take while on the study.
- you are not able to take the study drugs as required by the study.
- you do not have, or are not able to, have required study visits and evaluations

If you must stop taking the study drugs earlier than indicated by the study, the study doctor will ask you to remain on the study and complete the post discontinuation visits at 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 24 weeks from the date that you took the last dose of study treatment. Note that if you stop taking SOF, you must also stop taking RBV.

If I have to permanently stop taking study drugs through the study, or once I leave the study, how can I get study drugs?

If you must permanently stop taking SOF and RBV before the study is over, the study staff will talk with you about other options.

After you have finished the study, you will not be able to get SOF and RBV through the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm

Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this study and that social harm may result (because you could become labeled as being infected with HIV and/or HCV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Risks of Drawing Blood

Drawing blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Risks of Study Drugs

For those persons taking HIV medicines, there is no clear risk of drug interactions between HIV medicines and SOF. Although SOF has not been studied with all HIV medicines, it has been studied with all first-line HIV medication drug classes and there are no recognized clinically significant interactions.

Drug interactions that increase the levels of medicine in your blood may increase the chances of side effects. Drug interactions that lower the levels of SOF in your blood may decrease your chances for a cure of hepatitis C and/or cause drug resistance. To date only two out of over 3,000 patients have developed resistance to SOF, this risk is thought to be extremely low. Drug interactions that lower the levels of HIV medicines in your blood could cause drug resistance, meaning the drugs no longer work to prevent virus from reproducing.

Drug resistance may also prevent other medicines from working in the future. HIV viral load will be monitored regularly to ensure that evidence of early failure of the HIV regimen is identified quickly. In addition, multiple drug interactions studies have been completed to ensure that HIV medications can be safely dosed with SOF, and there is no evidence to suggest that concomitant dosing with SOF and any antiretroviral allowed in this study will lead to HIV regimen failure. The risk is thought to be very low.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Sofosbuvir (SOF)

- Depression
- Irritability
- Sleep disturbances
- Tiredness
- Muscle pain
- Headaches
- Chills
- Nausea and vomiting
- Stomach pain
- Rash
- Anemia
- Lymphopenia
- Itching
- Loss of appetite
- Diarrhea
- Dizziness
- Elevated liver function tests

Ribavirin (RBV)

- Anemia. Anemia can worsen existing heart and pulmonary (lung) conditions.
- Temporary changes in blood platelet levels
- Temporary changes in liver function tests (a measure of your liver activity)
- Stomach and intestinal
 - Nausea
 - Vomiting
 - Indigestion

- Stomach discomfort
- Skin disorders
- Upper respiratory tract inflammation
- Teratogenicity (risk to an unborn baby)
- Nervous system
 - Depression
 - Insomnia (inability to sleep)
 - Nervousness
 - Skin tingling
 - Drowsiness
 - Light-headedness
- Hyperuricemia (excess of uric acid in blood which can lead to gout, a painful swelling of joints and may lead to kidney disease).

NOTE: There are reports indicating that HIV-infected people taking treatment for HIV and HCV have developed high lactate (an acid that can build up in the bloodstream and cause life-threatening illness) levels with worsening liver disease. It is not clear if RBV is the cause. This may be more common if RBV is taken with didanosine (ddl, Videx) for HIV infection. There may be an increased risk of inflammation of the pancreas when didanosine is taken with RBV. Because of these risks, didanosine use is not allowed in this study.

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on HIV medications to enter this study. If you are not on HIV medications at the time of your HCV infection and you and your doctor do not think you need to start HIV medications, we will not exclude you from the study. We also do not recommend delaying HIV medications for entry into the study if your doctor feels they are medically necessary. Although the dosing period of the HCV medications is short, a delay in necessary HIV medications could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term after effects of HIV infection. If you have any concerns about these risks, we suggest that you discuss them with your provider.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant. Note that if you become pregnant or your partner becomes pregnant, study drugs will be stopped and you will be followed after delivery.

Because of the risk involved, you and your partner must use at least two methods of birth control that you discuss with the study staff. You must continue to use both methods until 6 months after stopping study drugs. You must choose two or more of the birth control methods listed below:

- A condom (male or female) with or without a spermicide

- Diaphragm or cervical cap with spermicide
- An intrauterine device (IUD)
- Tubal ligation
- Hormone-based contraceptives (except those containing drospirenone)

If you can become pregnant, you must have a pregnancy test within 72 hours before starting the study drugs. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits.

Some of the methods listed above may not prevent the spread of HIV to other people. You should discuss your contraceptive choices with your health care provider to choose the best way for you to both prevent pregnancy as required by this study and to prevent the spread of HIV to your partner.

If you think you or your partner may be pregnant at any time during the study, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study drugs, and counseling on RBV's teratogenicity (ability to cause birth defects). You will be followed on study, including male participants whose partners become pregnant, until study completion. You will be asked to return to the clinic 6 months after the end of your pregnancy to follow up on any side effects. Male participants whose partners become pregnant will have treatment discontinued and the same followup visit at 6 months after their partner's delivery as outlined for pregnant women. Pregnancies will be reported to the Ribavirin Pregnancy Registry. In addition, pregnancy complications and/or pregnancies outcomes will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you. Your health may be watched more closely than usual while you are on the study, which may help you to feel better. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and HCV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- treatment with prescription drugs currently available to you
- treatment with other experimental drugs, if you qualify
- no treatment; some people may clear the HCV infection on their own over the first year of infection, although over 9 in 10 people clear in the first 12 weeks of the new infection

Please talk to your doctor about these and other treatment choices available to you and the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protection, your site's institutional review board (a committee that makes sure that your rights and safety are protected while in the study), National Institutes of Health (NIH), study staff, study monitors, and other government agencies as part of their duties, and the pharmaceutical company supporting this study. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. [*Sites: Per US federal regulations, this language cannot be modified.*]

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drugs, the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[*Sites: Please indicate whether you will provide payment to subjects. If so, please describe the amount to be paid or reimbursed, the payment schedule, and any prorated schedule should the subject decide to withdraw or is withdrawn early by the investigator.*]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of taking part in this study, you will be given treatment right away for your injuries and be referred for further treatment, if necessary. However, you or your insurance company may have to pay for this care. There is no program for compensation either

through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not affect other studies done by NIH in which you may be taking part, and will not lead to any penalty or loss of benefits that you have the right to expect.

We will tell you about new information from this or other studies that may affect your health, welfare, or decision to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5327 **FOR COHORT 1**

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Subject's Name (print)

Subject's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff's Signature and Date

Witness's Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX III

**DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT FOR COHORT 2
For protocol: A5327**

**Final Version 2.0, 07/02/15: Sofosbuvir-Containing Regimens Without Interferon For
Treatment of Acute HCV in HIV-1 Infected Individuals (SWIFT-C)**

**SHORT TITLE FOR THE STUDY: A5327/SWIFT-C Final Version 2.0, 07/02/15, SOF
Regimens Without IFN For Treatment of Acute HCV Infection**

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV (the virus that causes AIDS) and you have also recently been infected with the hepatitis C virus (HCV, a virus that affects the liver). This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

People who are recently infected with HCV have a great chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being infected. This study is being done to see if a combination of two new drugs in one pill can replace the old drugs to provide a safer, more effective, and better tolerated treatment for new HCV infection. The names of the new drugs are ledipasvir (LDV) and sofosbuvir (SOF), and they will replace pegylated-interferon alfa (PEG-IFN, a drug given as a weekly injection under the skin) and ribavirin (RBV).

The fixed-dose combination of LDV and SOF (LDV/SOF) has been approved by the Food and Drug Administration (FDA) for the treatment of chronic HCV genotype 1 in people who do not have HIV. HCV genotype 1 is the most common HCV infection in the United States. LDV/SOF has also been studied in people with HIV and chronic HCV and was found to be safe and effective.

This study started with participants in Group 1 receiving SOF in combination with RBV, a drug also approved by the FDA, for 12 weeks. There were a total of 17 participants in

APPENDIX III (Cont'd)

Group 1 and all completed treatment. All participants were monitored for safety and viral response while on treatment. After completing treatment, all participants were evaluated for a treatment response after the end of treatment.

If the treatment response in Group 1 was high enough, the study design allowed for the possibility to decrease the length of therapy for Group 2 to 8 weeks, using the same treatment. However, this did not occur. Combined with the fact that a new and more effective treatment for chronic HCV has been approved since the study started, Group 2 will now receive 8 weeks of LDV/SOF instead of 12 weeks of SOF with RBV.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 27 people (men and women age 18 years and older) will take part in Group 2 of this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for approximately 32 weeks.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study, you will continue taking your current anti-HIV drugs if you are receiving them. If you are not currently on HIV medications and your provider does not think you need HIV medications during the study that is also acceptable. You will participate in Group 2 and will take LDV/SOF (a pill taken once daily by mouth) for 8 weeks. You will be given the medications at your study visits to take home, and you will need to store the medications in a safe place at room temperature. After you have completed 8 weeks of treatment with LDV/SOF, you will continue to have follow-up visits for 24 weeks.

Everyone who enters the study will take LDV/SOF, which will be given for free by the study. Anti-HIV drugs will not be provided by the study.

While you are in this study, you will need to be seen in the clinic about 10 times during the study. The study staff will tell you about how long each visit could be. You may need to come to the clinic if you have side effects or if you switch or take new anti-HIV drugs. More information about the study tests is given below. During the study, you will get the results from any routine tests that are done during the study when they are available.

You must fast for the screening, week 4 on-treatment, end of treatment (week 8), week 12 post treatment, and early treatment/study discontinuation visits. You may also have to fast for the entry visit; the study staff will inform you if you must fast for the entry visit. (Fasting means that you should not eat or drink anything for at least 8 hours before your visit. You may only drink water and take your prescription medications during this time.

APPENDIX III (Cont'd)

If your medications require food, the study staff will talk to you about how you should take your medications.) The study staff will remind you to fast before each of these study visits. If you do not fast before these visits, you will be asked to come back later for these tests after fasting.

If you do not enroll into the study

If you decide not to take part in this study or if you do not qualify to take part in this study, we will still use some of your information. As part of the screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ T-cell count, viral load) information is being collected from you so that ACTG researchers may see if there are patterns or common reasons why people do not join a study.

Required Tests

Your blood will be drawn from a vein in your arm and used to measure your HCV and HIV viral load (the amount of HCV and HIV in your blood) and genotype (genetic makeup of the virus), to measure your CD4+/CD8+ cell counts (these are cells in your blood that fight infection), to measure levels of certain hormones (hormones are chemicals in your blood), and for routine safety tests and metabolic tests (to test how your body uses the food that you eat). You will also have a urine test. You will be told the results of these tests when they become available.

Some of your blood will also be stored (with no information that will identify you) and used for future HCV/HIV resistance tests required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications. In addition, some of this blood will be used to understand how the drugs interact with your body and how your body responds to the drugs.

Any remaining blood will be stored for future testing required by the study.

Additional Tests

If you agree, your blood will be drawn and used for future testing. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your blood used for future ACTG-approved research. You may change your mind at any time and your samples will be destroyed.

_____ YES _____ NO

Genetic (the message in your DNA) testing

If you agree, your blood will be drawn and used to examine different genes (pieces of your DNA). Results of testing done on these samples may not be given to you because they will be done in the future.

APPENDIX III (Cont'd)

Please initial below if you agree to have any of your blood used for ACTG-approved genetic testing. You may change your mind at any time and your samples will be destroyed.

_____ YES _____ NO

Optional Tests

If you agree, any blood left over after all required study testing is done may be stored (with no information that will identify you) and used for future ACTG-approved research. These blood samples may be stored for an unknown period of time. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your leftover blood used for future ACTG-approved research. You may change your mind at any time and reasonable efforts will be made to destroy your samples, though this may not always be possible.

_____ YES _____ NO

A5327 Group 2 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Study Schedule

Evaluation or test	Screen	Pre-Entry	Entry	Post-Entry Visits			Other Visits	Early discontinuation
				On-treatment Visits	End of treatment	Off-treatment Visits		
Consent	✓							
Clinical assessments	✓		✓	✓	✓	✓		✓
ECG	✓							
Samples collection & laboratory testing	✓	If required	✓	✓	✓	✓	✓	✓
Urine sample			✓	✓	✓	✓		✓
Pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓
Pharmacokinetic (PK) studies			✓	✓	✓	✓	✓	✓
Pregnancy prevention counseling			✓	✓	✓	✓		✓

APPENDIX III (Cont'd)

Evaluation or test	Screen	Pre-Entry	Entry	Post-Entry Visits			Other Visits	Early discontinuation
				On-treatment Visits	End of treatment	Off-treatment Visits		
Adherence assessments				✓	✓			✓
Study drugs distribution and storage			✓					

II. Description of Study Visits

Screening

After you have read and signed the consent form, you will be asked questions about your health, medical history, and medication history. You will have several tests, including blood tests, to make sure that you qualify to join the study. Some of the blood taken will be shipped to a testing lab. Your new HCV infection and how long you've been infected will be confirmed. You must come to the visit fasting. If you are not fasting within the past 8 hours before this visit, you will be asked to come back fasting. Also, an electrocardiogram (ECG) will be done at this visit.

If you are a female, you will have blood or urine taken for pregnancy testing.

Pre-entry

You may be asked to return to the study clinic to have a repeat HCV viral load to confirm that you still have the infection. If you do still have the infection, you will come back for the entry visit. If you do not have evidence of ongoing infection, you will not enter the study. You will be referred back to your doctor for followup to ensure the virus does not come back. If you are a female, you will have blood or urine taken for pregnancy testing.

Entry

When all of the results from your screening tests are available, you will come back to the clinic to have a few tests done before starting the study. You will have urine and blood samples collected for routine safety tests. If you are a female, you will be asked to provide blood or urine sample for pregnancy testing. You may need to come to the clinic fasting for this visit (fasting means that you should not eat or drink anything for at least 8 hours before your visit). The study staff will inform you before the entry visit if you have to be fasting. If you are not fasting within the past 8 hours before this visit, you will be asked to come back fasting.

At this visit, you will get your study drugs. The study staff will give you enough study drugs to last until the week 8 visit. You do not need to take the study drugs with food. If you forget to take the study drugs at the correct time, it may be taken later in the day. Then the next day you should continue with the usual schedule that you take the study drugs. You should never cut or split your study medications.

You will have an extra evaluation (pharmacokinetic [PK] testing) done at the entry visit. This evaluation is described below.

Post-entry visits

You will be seen at treatment weeks 1, 2, 4, and 8 (end of treatment) AND at post-treatment weeks 2, 4, 8, 12, and 24 after taking the last dose of study drugs. These visits will last about 1-1½ hours each.

You must return any remaining study drug during the post-treatment visits.

If you are a woman, you will be asked to provide blood or urine sample for pregnancy testing.

Other visits

During the study, you may have to come back to the clinic for extra visits for testing of any lab results that are not normal, or to followup on a specific side effect or symptom.

Virologic Failure Confirmation

If laboratory tests show there is evidence of virologic failure (which is detectable HCV when you were previously undetectable or your virus has not gone down as quickly as expected), you will be asked to return to the clinic to confirm your lab results. If virologic failure is confirmed, you will then complete an early discontinuation study visit as described below.

Early discontinuation

There are two types of discontinuation (stopping study treatment or leaving the study early) in which you will be asked to come to the clinic for an extra visit in a fasting state.

1. Stop study treatment early

You or your doctor may decide to stop the study medication that you began at entry.

If you must stop taking the study medication early, the study doctor may ask you to stay in the study and come in for some tests.

2. Leave study early

You or your doctor decides that you will no longer stay in the study or you are notified the study is stopped early. You will be asked to complete some evaluations before being taken off the study.

APPENDIX III (Cont'd)

III. Description of Study Evaluations

Consent

After you read the consent form and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be tested to see if you qualify for the study.

Clinical Assessments

You will have the following clinical evaluations in this study:

Physical examination

You will have a physical exam. The study staff will check the different systems in your body such as head, neck, eyes, ears, nose, throat, mouth and tongue, chest (excluding breasts) for respiratory, heart for cardiovascular, abdomen, skin, hair, nails, and muscles and joints. The study staff will also check your vital signs such as temperature, pulse, blood pressure, and respiratory rate, and your height and weight will be recorded.

Medical and medication history

You will be asked questions about your health and about any medicines you have taken or are taking now. Once you are on treatment, you will be asked about any signs or symptoms that you are experiencing and any changes in other medications that you have had since your last visit.

Electrocardiogram

You will have an electrocardiogram (ECG) done. An ECG is a test to measure the heartbeat. An ECG machine will be used to do an electrical tracing of your heart that can show how hard it is working. You will have to lie very still for at least 5 minutes while the ECG is being done.

Sample collections and laboratory testing

You will have the following samples collected and tested in this study:

Blood collected

Blood will be taken from a vein in your arm for various tests during the study. Approximately 144 mL (10 tablespoons) of blood will be drawn during any study visit. These may include: routine safety lab tests such as kidney and liver function, HIV viral load (a test that shows how much HIV is in your blood), CD4+/CD8+ counts (a test that shows how many infection-fighting cells you have in your blood), HCV viral load (a test that shows how much HCV is in your blood).

You will be asked to fast before some of the visits. This means that you should not eat or drink anything except prescription drugs and water for at least 8 hours before the visit.

APPENDIX III (Cont'd)

Resistance testing

Blood will be drawn and stored for future HCV/HIV resistance testing that is required for this study. A resistance test is used to determine if the HCV/HIV viruses still respond to your medications.

Genetic testing

If you agree blood will be drawn for testing your genes (pieces of your DNA) to understand if you naturally were born with a better or worse chance of responding to the medications. Some of your blood cells will also be tested to see if your responsiveness to the therapy is associated with different genes related to IFN use. An IFN is an antiviral compound that is produced in response to many types of infections. You will not receive the results of these studies because they will be done in the future.

PK Studies

Blood will be drawn to measure the levels of the study drugs in your blood and to understand how the drugs interact with your body and how your body responds to the drugs.

Urinalysis

Urine samples will be collected for routine safety tests.

Pregnancy test

If you are a woman, you will have blood or urine taken prior to study entry. After you enter the study, you will be asked to provide blood or urine samples for pregnancy testing.

Pregnancy prevention counseling

All participants, male and female, will be counseled on the risk of the study drugs in pregnancy and on how to prevent pregnancy.

Adherence assessments

You will be asked about how well you take your medications. The study staff will give you information and encouragement to help you take your medications as prescribed.

Study drugs distribution and storage

You will be given an 8-week supply of study drugs at entry. You will be asked to store the study drugs as instructed on the medicine bottle label.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is cancelled.
- a Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study for safety).
- your doctor thinks the study is no longer in your best interest.

APPENDIX III (Cont'd)

- the site investigator thinks that you are at significant risk of failing to comply with the requirements of the protocol.

The study doctor may also need to take you off the study drugs without your permission if:

- you experience HCV treatment failure.
- you become pregnant.
- you are breastfeeding.
- continuing the study drugs may be harmful to you.
- you need a treatment that you may not take while on the study.
- you are not able to take the study drugs as required by the study.
- you do not have, or are not able to, have required study visits and evaluations

If you must stop taking the study drugs earlier than indicated by the study, the study doctor will ask you to remain on the study and complete the post discontinuation visits at 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 24 weeks from the date that you took the last dose of study treatment.

If I have to permanently stop taking study drugs through the study, or once I leave the study, how can I get study drugs?

If you must permanently stop taking study drugs before the study is over, the study staff will talk with you about other options.

After you have finished the study, you will not be able to get FDC LDV/SOF through the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm

Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this study and that social harm may result (because you could become labeled as being infected with HIV and/or HCV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Risks of Drawing Blood

Drawing blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Risks of Study Drugs

Drug interactions that increase the levels of medicine in your blood may increase the chances of side effects. Drug interactions that lower the levels of HIV medicines in your blood could cause drug resistance, meaning the drugs no longer work to prevent virus from reproducing. Drug interactions that lower the levels of SOF or LDV in your blood may decrease your chances for a cure of hepatitis C and/or cause drug resistance.

APPENDIX III (Cont'd)

Bradycardia, or slow heart rate, may happen in persons who are taking amiodarone (a medicine that is used to treat heart rhythm problems) particularly for those also taking beta blockers (medications that reduce blood pressure) or those with a heart disorder and/or advanced liver disease. Because of this risk it is not recommended to take LDV/SOF with amiodarone and persons taking amiodarone will not be allowed to participate in this study. It is also not recommended to take LDV/SOF with other medicines that contain SOF.

For those persons taking HIV medicines, there is no clear risk of drug interactions between HIV medicines and SOF. Although SOF has not been studied with all HIV medicines, it has been studied with all first-line HIV medication drug classes and there are no recognized clinically significant interactions. This is also true for LDV with the exception of one of the HIV medications named tenofovir (TFV). LDV increases TFV levels in your body. With most other HIV drug combinations this increase is not felt to lead to significant risk unless your kidneys don't work normally. However, if TFV and LDV are used with HIV protease inhibitors that are combined with ritonavir (RTV) or with a drug named cobicistat (COBI), that is not an HIV drug but is used to increase the level of your HIV drugs in your blood stream, the potential risk of kidney toxicity may be higher. The combination of HIV protease inhibitors or COBI and LDV and TFV has not been studied in HIV-infected patients. For this reason there will be monitoring of the kidney function for all participants in this study.

Drug resistance may prevent other medicines from working in the future. HIV viral load will be monitored regularly to ensure that evidence of early failure of the HIV regimen is identified quickly. In addition, multiple drug interactions studies have been completed to ensure that HIV medications can be safely dosed with SOF, and there is no evidence to suggest that giving SOF or LDV and any antiretroviral allowed in this study will lead to HIV regimen failure. The risk is thought to be very low. To date only two out of over 3,000 patients have developed resistance to SOF, so this risk is also thought to be extremely low. Risk of resistance to LDV is high for patients who fail therapy, with most patients developing resistance. At this time the effect of resistance to LDV or similar medications is not clear, but it may increase the risk of other HCV treatments not working.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Sofosbuvir (SOF) or Ledipasvir/sofosbuvir (LDV/SOF)

- **Depression**

APPENDIX III (Cont'd)

- Irritability
- Sleep disturbances
- Tiredness
- Muscle pain
- Headaches
- Chills
- Nausea and vomiting
- Stomach pain
- Rash
- Anemia
- Lymphopenia
- Itching
- Loss of appetite
- Diarrhea
- Dizziness
- Elevated liver function tests

ARE THERE RISKS RELATED TO DELAYING HIV THERAPY?

You are not required to be on HIV medications to enter this study. If you are not on HIV medications at the time of your HCV infection and you and your doctor do not think you need to start HIV medications, we will not exclude you from the study. We also do not recommend delaying HIV medications for entry into the study if your doctor feels they are medically necessary. Although the dosing period of the HCV medications is short, a delay in necessary HIV medications could allow for progression of HIV disease, which can increase your risk of opportunistic infections and long-term after effects of HIV infection. If you have any concerns about these risks, we suggest that you discuss them with your provider.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs or drug combinations in this study may be unsafe for unborn babies. Although there is no evidence that these medications can result in birth defects, it is not recommended that you get pregnant during therapy. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Note that if you become pregnant, study drugs will be stopped and you will be followed after delivery.

Because of the potential risk involved and due to the uncertainty of risk to the fetus, you and your partner must use at least two methods of birth control that you discuss with the study staff. You must continue to use both methods until 6 months after stopping study drugs. You must choose two or more of the birth control methods listed below:

- A condom (male or female) with or without a spermicide
- Diaphragm or cervical cap with spermicide
- An intrauterine device (IUD)

- Tubal ligation
- Hormone-based contraceptives

If you can become pregnant, you must have a pregnancy test within 72 hours before starting the study drugs. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits.

Some of the methods listed above may not prevent the spread of HIV to other people. You should discuss your contraceptive choices with your health care provider to choose the best way for you to both prevent pregnancy as required by this study and to prevent the spread of HIV to your partner.

If you think you may be pregnant at any time during the study, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study drugs. You will be followed on study until study completion. You will be asked to return to the clinic 6 months after the end of your pregnancy to follow up on any side effects. In addition, pregnancy complications and/or pregnancies outcomes will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you. Your health may be watched more closely than usual while you are on the study, which may help you to feel better. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and HCV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- treatment with prescription drugs currently available to you
- treatment with other experimental drugs, if you qualify
- no treatment; some people may clear the HCV infection on their own over the first year of infection, although over 9 in 10 people clear in the first 12 weeks of the new infection

Please talk to your doctor about these and other treatment choices available to you and the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such

APPENDIX III (Cont'd)

as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protection, your site's institutional review board (a committee that makes sure that your rights and safety are protected while in the study), National Institutes of Health (NIH), study staff, study monitors, and other government agencies as part of their duties, and the pharmaceutical company supporting this study. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drugs, the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[Sites: Please indicate whether you will provide payment to participants. If so, please describe the amount to be paid or reimbursed, the payment schedule, and any prorated schedule should the participant decide to withdraw or is withdrawn early by the investigator.]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of taking part in this study, you will be given treatment right away for your injuries and be referred for further treatment, if necessary. However, you or your insurance company may have to pay for this care. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not affect other studies done by NIH in which you may be taking part, and will not lead to any penalty or loss of benefits that you have the right to expect.

We will tell you about new information from this or other studies that may affect your health, welfare, or decision to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- **name of the investigator or other study staff**
- **telephone number of above**

For questions about your rights as a research participant, contact:

- **name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site**
- **telephone number of above**

SIGNATURE PAGE ACTG Study A5327 FOR COHORT 2

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

**Study Staff Conducting
Consent Discussion (print)**

Study Staff's Signature and Date

**Witness's Name (print)
(As appropriate)**

Witness's Signature and Date